(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 January 2001 (04.01.2001)

PCT

(10) International Publication Number
WO 01/00229 A1

(51) International Patent Classification[7]: A61K 38/19, 31/63

(21) International Application Number: PCT/US00/16292

(22) International Filing Date: 26 June 2000 (26.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/141,238 24 June 1999 (24.06.1999) US

(71) Applicant *(for all designated States except US)*: **PHARMACIA CORPORATION** [US/US]; P.O. Box 5110, Chicago, IL 60680-5110 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **KEANE, J., Timothy** [US/US]; 66 Broadview Drive, Clayton, MO 63105 (US).

(74) Agents: **WILLIAMS, Roger, A.**, et al.; Pharmacia Corporation, Corporate Patent Department, P.O. Box 5110, Chicago, IL 60680 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/00229 A1

(54) Title: COMBINATION OF TUMORS NECROCIS FACTOR (TNF) ANTAGONISTS AND COX-2 INHIBITORS FOR THE TREATMENT OF INFLAMMATION

(57) Abstract: The present invention provides combinations of a tumor necrosis factor antagonizing agent and a cyclooxygenase-2 inhibiting agent for treating inflammatory disease in a mammal.

COMBINATION THERAPY FOR THE TREATMENT OF INFLAMMATORY DISEASES

This application claims priority under 35 USC §119(e) of United States provisional application Serial No. 60/141,238, filed June 24, 1999.

Description

Field of the Invention

The present invention relates to methods for treating an inflammatory disease in a mammal using a tumor necrosis factor antagonist and a selective cyclooxygenase-2 inhibitor.

Background of the Invention

Rheumatoid arthritis (RA) is estimated to occur in one to three percent of the general population and is one of the most common causes of disability. There is no known cure for rheumatoid arthritis and current disease modifying antirheumatic drugs (DMARDs) fail to address the underlying cause of the disease. Current rheumatoid arthritis treatment consists predominantly of symptomatic relief by administration of non-steroidal anti-inflammatory drugs (NSAIDs). NSAID treatment is mainly effective in the early stages of rheumatoid arthritis, and is unlikely to produce suppression of joint inflammation if the disease is present for more than one year. Gold, methotrexate, immunosuppressants and corticosteroids have been tried with limited success. In advanced cases of rheumatoid arthritis, the traditional methods of treatment have generally been aimed at avoiding toxicity.

Disease modifying antirheumatic drugs also play a predominant role in the treatment of rheumatoid arthritis, but their toxicological profile limits their application and effectiveness in long-term therapy. For example, methotrexate (MTX) has demonstrated long-term efficacy, but its toxicological profile, e.g., gastrointestinal upset, mucosal ulcerations, renal impairment, pulmonary toxicity, is the most common

reason cited among patients for treatment termination. The toxicity profile of MTX remains a major concern among physicians and prolonged treatment with MTX may require invasive biopsy procedures in a patient to monitor hepatic function.

Another disease modifying antirheumatic drug, sulfasalazine, has been shown to be more effective than hydroxychloroquine in the treatment of rheumatoid arthritis, but it is not as well tolerated, with 20% of patients terminating treatment due to adverse gastrointestinal side effects. Azathioprine, penicillamine and gold compounds have also been shown to be efficacious in treating rheumatoid arthritis, but are not as well tolerated as MTX, sulfasalazine or hydroxychloroquine. Cylcosporine has shown applicability in treating rheumatoid arthritis, but its renal toxicity has limited its usage to salvage therapy or in combination therapy with other disease modifying antirheumatic drugs. Thus, treating rheumatoid arthritis with disease modifying antirheumatic drugs remains complicated by poor efficacy and the occurrence of adverse side effects. Lack of predictability of these adverse reactions has made regular monitoring of a patients physiological condition mandatory where long term therapy is anticipated. Such monitoring include, for example, measuring blood count, and/or performing liver, kidney, urine or ophthalmologic tests.

Historically, treatment of the inflammatory actions was available through the use of non-steroidal anti-inflammatory drugs (NSAIDs). This class of drugs possesses anti-inflammatory, analgesic and anti-pyretic activity, and are widely used to treat chronic inflammatory states such as arthritis. However, common NSAIDs that are active in reducing the PG-induced pain and swelling associated with the inflammation process are also active in affecting the other PG-roles which is not associated with the inflammation process. Thus, use of high doses of most common NSAIDs can produce severe side effects, including life threatening ulcers, that limit their therapeutic potential. An alternative to NSAIDs is the use of corticosteroids, which have even more drastic side effects, especially when long term therapy is involved.

Prostaglandins (PGs) play a major role in the inflammation process and the inhibition of prostaglandin production, especially production of PGG_2, PGH_2 and PGE_2, has been a common target of anti-inflammatory drug discovery. Along with

this role, PGs play a cytoprotective role in the gastrointestinal tract and also on renal function.

Previous NSAIDs have been found to prevent the production of PGs by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway, including the enzyme cyclooxygenase (COX). The recent discovery of an inducible enzyme associated with inflammation (named "cyclooxygenase-2" or "COX-2" or "PGHS-2" or "prostaglandin G/H synthase II") provides a viable target of inhibition which more effectively reduces inflammation and produces fewer and less drastic side effects.

Compounds which selectively inhibit cyclooxygenase-2 have been described, for example, in U.S. patents 5,380,738; 5,344,991; 5,393,790; 5,466,823; 5,434,178; 5,474,995 and 5,510,368; and WO documents WO 96/06840; WO 96/03388; WO 96/03387; WO 95/15316; WO 94/15932; WO 94/27980; WO 95/00501; WO 94/13635; WO 94/20480 and WO 94/26731.

Cytokines are signaling peptide molecules that modulate a wide variety of cellular functions that includes inflammation. Cellular response occurs as a result of interaction between a particular cytokine and high-affinity cell-surface receptors specific for each cytokine. The receptor-binding event leads to the transduction of a signal across the cell membrane and the activation of intracellular biochemical pathways and gene translation or transcription events.

Tumor Necrosis Factor-alpha (TNF-a) is a cytokine produced primarily by activated monocytes and macrophages. Excessive or unregulated tumor necrosis factor production has been implicated in mediating a number of diseases. Recent studies indicate that tumor necrosis factor has a causative role in the pathogenesis of rheumatoid arthritis. Additional studies demonstrate that inhibition of tumor necrosis factor has broad application in the treatment of inflammation, inflammatory bowel disease, multiple sclerosis and asthma.

Tumor necrosis factor has also been implicated in viral infections, such as HIV, influenza virus, and herpes virus including herpes simplex virus type-1 (HSV-1), herpes simplex virus type-2 (HSV-2), cytomegalovirus (CMV), varicella-zoster virus (VZV), Epstein-Barr virus, human herpesvirus-6 (HHV-6), human herpesvirus-7 (HHV-7), human herpesvirus-8 (HHV-8), pseudorabies and rhinotracheitis, among others.

Interleukin-8 (IL-8) is another pro-inflammatory cytokine, which is produced by mononuclear cells, fibroblasts, endothelial cells, and keratinocytes, and is associated with conditions including inflammation.

Interleukin-1 (IL-1) is produced by activated monocytes and macrophages and is also involved in the inflammatory response. IL-1 plays a role in many pathophysiological responses including rheumatoid arthritis, fever and reduction of bone resorption.

Tumor necrosis factor receptor, IL-1 and IL-8 affect a wide variety of cells and tissues and are important inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines is of benefit in controlling, reducing and alleviating many of these disease states. Modulation of cytokine response is achieved by blocking cytokine receptors with small molecules, altering the cytokine to reduce its affinity to its receptor, or by downregulating the expression of cytokines.

Rau R. et al., (J. Rheumatol. (1998), 25(8), 1485-1492), describe a combination of methotrexate (MTX) and parenteral gold or MTX and other disease modifying antirheumatic drugs (DMARD) in the treatment of rheumatoid arthritis.

Conagham P. and P. Brooks (Curr. Opin. Rheumatol. (1996), 8(3), 176-182), describe methotrexate in combination therapy with intramuscular gold and other DMARDs for the treatment of arthritis.

Furst D., (J. Rheumtol., Suppl. (1996) 44 (Rheumatoid Arthritis: The Status and Future of Combination Therapy), 86-90), reviews 16 references and describes an approach to rheumatoid arthritis disease modifying drug combination therapy.

Li E., (Curr. Opin, Rheumatol. (1998), 10(3), 159-168), describes certain disease modifying antirheumatic drugs in combination therapy in patients suffering from rheumatoid arthritis.

Conagham P., et al., (Curr. Opin. Rheumatol. (1997) 9(3), 183-190), describes MTX, sulfasalazine, and hydroxychloroquine in combination therapy for the treatment of rheumatoid arthritis.

O'Dell J., et al., (J. Rheumatol. Suppl. (1996), 44 (Rheumatoid Arthritis: The Status and Future of Combination Therapy), 72-4), describe the single agent therapy of MTX, sulfasalazine or hydroxychloroquine and the combination of MTX, sulfasalazine and hydroxychloroquine, and MTX in combination with either sulfasalazine or hydroxychloroquine.

Dijkmans B., et al., (J. Rheumatol. Suppl. (1996), 44, 23:61-63), describes a 2 phase study using a combination of cyclosporin A (CsA) (an inhibitor of interleukin 2 (IL-2) and other cytokine production) with chloroquine for the treatment of rheumatoid arthritis.

U.S. Patent No. 5,700,816 describes the treatment of inflammation and inflammation-related disorders with a combination of a selective cyclooxygenase-2 inhibitor and a leukotriene A4 hydrolase inhibitor.

U.S. Patent No. 5,859,041 describes a class of substituted imidazoles and its use in preventing cytokine mediated disease by inhibiting cytokine activity.

U.S. Patent No. 5,772,992 describes compositions comprising a human interleukin-3 variant or mutant protein and another colony stimulating factor, cytokine, lymphokine, interleukin, or hematopoietic growth factor.

U.S. Patent No. 5,864,036 describes a class of 1,4,5-substituted imidazole compounds and their use in treating cytokine mediated diseases.

U.S. Patent No. 5,633,272 describes substituted isoxazoles used in co-therapy for the treatment of inflammation, with conventional antiinflammatories.

U.S. Patent No. 5,512,544 describes tumor necrosis factor binding proteins useful in the treatment of autoimmune disease and graft-versus-host reactions.

U.S. Patent No. 5,698,195 describes anti-tumor necrosis factor antibodies useful in the treatment of, inter alia, chronic inflammatory diseases, and autoimmune disease.

WO document WO 91/03553, describes treating TNF-dependent inflammatory disease, such as arthritis, by administrating tumor necrosis factor receptor protein with a interleukin-1 receptor and/or interleukin-2 receptor.

U.S. Patent No. 5,563,165 describes pyrazolyl benzenesulfonamide compounds and their use in treating inflammation and inflammation-related disorders.

US Patent No. 5,605,690 describes a method for treating TNF-dependent inflammatory diseases in a mammal by administering a tumor necrosis factor antagonist, and particularly pointing to a TNF-receptor.

WO document WO 98/06708, describes a crystalline form of 4-[5-methyl-3-phenylosoxazol-4-yl]benzenesulfonamide in co-therapy with steroids, NSAIDs, 5-lipooxygenase inhibitors, LTB_4 receptor antagonists and LTA_4 hydrolase inhibitors, used in treating cyclooxygenase-2 associated disorders, including inflammation.

U.S. Patent No. 5,633,273 describes the use of substituted isoxazoles in co-therapy with steroids, NSAIDs, 5-lipooxygenase inhibitors, LTB_4 receptor antagonists and LTA_4 hydrolase inhibitors, for the treatment of inflammation and inflammation related disorders, such as arthritis.

U.S. Patent No. 5,869,471 describes the administration of NSAIDs and bone-active phosphonates for the treatment of arthritis.

U.S. Patent No. 5,795,967 describes neutralizing antibodies directed against tumor necrosis factor used to suppress inflammatory immune-potentiated events, such as suppressing transplantation immunity and treating autoimmune diseases.

U.S. Patent No. 5,306,732 describes vinigrol, a tumor necrosis factor antagonist useful in the treatment of, inter alia, inflammation.

U.S. Patent No. 5,672,347 describes tumor necrosis factor antagonists useful for treating inflammation, and in particular the use of neutralizing antibodies directed against tumor necrosis factor in mediating immune-potentiated inflammatory events.

Description of the Invention

It has been found that the administration of a selective cyclooxygenase-2 inhibiting agent and a tumor necrosis factor antagonizing agent, for example, etanercept (ENBREL®; Immunex Corp), not only results in reduction of inflammation in patients suffering from inflammatory disease, but also maintains and/or increases the range of motion of joints in patients suffering from arthritic disease. The methods, combinations and compositions of the present invention provide effective therapy for treating inflammatory and arthritic disorders, for example, rheumatoid arthritis, with reduced adverse side effects as compared to such methods known in the art.

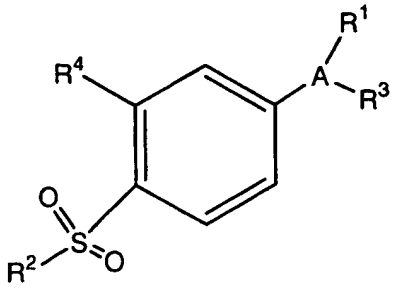
The method comprises treating an inflammatory disorder in a mammal in need thereof, by administering to the mammal a tumor necrosis factor antagonizing agent and a selective cyclooxygenase-2 inhibiting agent. Together the tumor necrosis factor antagonizing agent and the selective cyclooxygenase-2 inhibiting agent comprise an inflammatory disorder effective amount of the agents.

Tumor necrosis factor antagonizing agents useful in the present invention include proteins, or biologically active equivalents thereof, that competitively bind to a cell surface tumor necrosis factor receptor or an intracellular tumor necrosis factor

receptor. In one embodiment of the present invention the tumor necrosis factor antagonizing agent is etanercept, or a biologically active equivalent thereof

Other tumor necrosis factor antagonizing agents useful in the present invention include 2-[(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)methylene]-undecanoic acid; lenercept; BB-2275; PCM-4; SH-636; onercept; TBP-1; solimastat; MDL-201112; AGT-1; vinigrol; D-609; 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-pyrrolidinone; CytoTAb®; and Infliximab; or a biologically active equivalent thereof.

A class of selective cyclooxygenase-2 inhibiting agents useful in the present invention include compounds of Formula 1:



1.

wherein A is a 5- or 6-member ring substituent selected from partially unsaturated or unsaturated heterocyclo and carboxcyclic rings, wherein A is optionally substituted with one or more radicals selected from alkyl, halo, oxo, and alkoxy;

wherein R^1 is selected from cyclohexyl, pyridinyl, and phenyl, wherein cyclohexyl, pyridinyl, or phenyl are optionally substituted with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, phenylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio;

wherein R^2 is selected from alkyl and amino;

wherein R^3 is a radical selected from halo, alkyl, alkenyl, alkynyl, aryl, heteroaryl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, phenyl, haloalkyl, heterocyclo, cycloalkenyl, phenylalkyl, heterocyclylalkyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, phenylcarbonyl, phenylalkylcarbonyl, phenylalkenyl, alkoxyalkyl, phenylthioalkyl, phenylyloxyalkyl, alkoxyphenylalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-phenylaminocarbonyl, N-alkyl-N-phenylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-arylkylamino, N-

alkyl-N-arylkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-phenylaminoalkyl, N-phenylalkylaminoalkyl, N-alkyl-N-phenylalkylaminoalkyl, N-alkyl-N-phenylaminoalkyl, phenyloxy, phenylalkoxy, phenylthio, phenylalkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-alkyl-N-phenylaminosulfonyl; and

wherein R^4 is selected from hydrido and halo;

or a pharmaceutically-acceptable salt thereof.

The methods, combinations and compositions of the present invention can be useful for the treatment or prevention of inflammatory and arthritic disorders in a mammal including, but not limited to, disorders such as:

rheumatoid arthritis (RA); osteoarthritis (OA); spondylarthropy; ankylosing spondylitis; psoriatic arthritis; reactive arthritis; IBD related arthritis; undifferentiated spondyloarthropathy; Reider's syndrome; systemic lupus erythematosus; Behcet's disease; eosinophilia fasciitis; eosinophila-myalgia syndrome; familial Mediterranean fever; hereditary angioedema; juvenile chronic arthritis; palindromic rheumatism; idiopathic polymyositis; dermatomyositis; inclusion body myositis; systemic sclerosis; atherosclerosis; sarcoidisis; Reynaud's phenomenon; Sjogren's syndrome; Still's disease; systemic rheumatoid vasculitis; vasculitis; Wegener's granulomatosis; Whipple's disease; and xerostomia.

The present invention preferably includes compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. In one embodiment, the compounds have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and in another embodiment have a selectivity ratio of at least 100. Such selectivity ratios may indicate an ability to reduce the incidence of common NSAID-induced side effects.

Within Formula 1 there is a subclass of compounds of particular interest wherein A is selected from thienyl, oxazolyl, furyl, furanone, pyrrolyl, thiazolyl, imidazolyl, benzofuryl, indenyl, benzithienyl, isoxazolyl, pyrazolyl, cyclopentenyl, cyclopentadienyl, benzindazolyl, cyclopentenone, benzopyranopyrazolyl, phenyl, and pyridyl;

wherein R^1 is selected from cyclohexyl, pyridinyl, and phenyl, wherein cyclohexyl, pyridinyl, or phenyl is substituted with one or more radicals selected from

C_{1-2} alkyl, C_{1-2} haloalkyl, cyano, carboxyl, C_{1-2} alkoxycarbonyl, hydroxyl, C_{1-2} hydroxyalkyl, C_{1-2} haloalkoxy, amino, C_{1-2} alkylamino, phenylamino, nitro, C_{1-2} alkoxy-C_{1-2}-alkyl, C_{1-2} alkylsulfinyl, C_{1-2} alkoxy, halo, alkoxy, and C_{1-2} alkylthio;

wherein R^2 is selected from alkyl and amino;

wherein R^3 is a radical selected from halo, C_{1-2} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, aryl, heteroaryl, oxo, cyano, carboxyl, cyano-C_{1-3}-alkyl, heterocyclyloxy, C_{1-3} alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, phenyl, C_{1-3} haloalkyl, heterocyclo, cycloalkenyl, phenyl-C_{1-3}-alkyl, heterocyclyl-C_{1-3}-alkyl, C_{1-3} alkylthio-C_{1-3}-alkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxycarbonyl, phenylcarbonyl, phenyl-C_{1-3}-alkylcarbonyl, phenyl-C_{2-3}-alkenyl, C_{1-3} alkoxy-C_{1-3}-alkyl, phenylthio-C_{1-3}-alkyl, phenylyloxyalkyl, alkoxyphenylalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonyl-C_{1-3}-alkyl, C_{1-3} alkylaminocarbonyl, N-phenylaminocarbonyl, N-C_{1-3} alkyl-N-phenylaminocarbonyl, C_{1-3} alkylaminocarbonyl-C_{1-3}-alkyl, carboxy-C_{1-3}-alkyl, C_{1-3} alkylamino, N-arylamino, N-arylkylamino, N-C_{1-3} alkyl-N-arylkylamino, N-C_{1-3} alkyl-N-arylamino, amino-C_{1-3}-alkyl, C_{1-3} alkylaminoalkyl, N-phenylamino-C_{1-3}-alkyl, N-phenyl-C_{1-3}-alkylaminoalkyl, N-C_{1-3} alkyl-N-phenyl-C_{1-3}-alkylamino-C_{1-3}-alkyl, N-C_{1-3} alkyl-N-phenylamino-C_{1-3}-alkyl, phenyloxy, phenylalkoxy, phenylthio, phenyl-C_{1-3}-alkylthio, C_{1-3} alkylsulfinyl, C_{1-3} alkylsulfonyl, aminosulfonyl, C_{1-3} alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-C_{1-3} alkyl-N-phenylaminosulfonyl; and

wherein R^4 is selected from hydrido and halo;

or a pharmaceutically-acceptable salt thereof.

Another class of compounds within Formula 1 of even more interest include compounds wherein A is substituted with one or more radicals selected from alkyl, halo, oxo, and alkoxy;

wherein R^1 is selected from pyridyl, cyclohexyl, and phenyl, wherein pyridyl, cyclohexyl, or phenyl is optionally substituted with one or more radicals selected from alkyl, halo, and alkoxy;

wherein R^2 is C_{1-2} alkyl or amino;

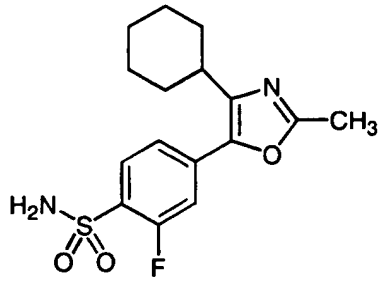
wherein R^3 is a radical selected from halo, C_{1-2} alkyl, cyano, carboxyl, C_{1-2} alkyloxy, phenyl, C1-2 haloalkyl, and C_{1-2} hydroxyalkyl; and

wherein R^4 is selected from hydrido and fluoro;

or a pharmaceutically-acceptable salt thereof.

A family of specific compounds within Formula 1 of particular interest include compounds and pharmaceutically-acceptable salts thereof, as follows:

C1)



4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide;

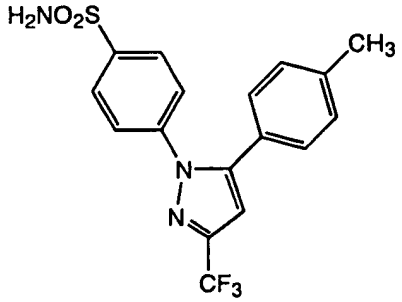
C2)

5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine;

C3)

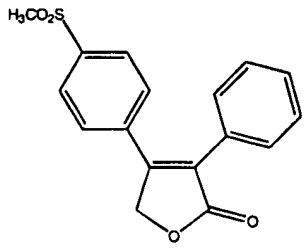
2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one;

C4)



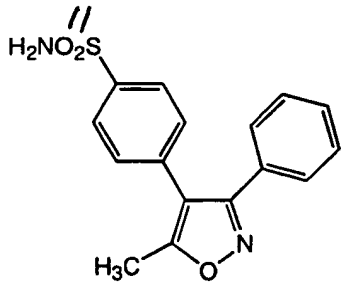
4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide;

C5)



4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone;

C6)

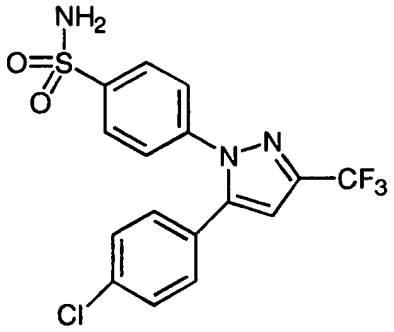


4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide;

C7)

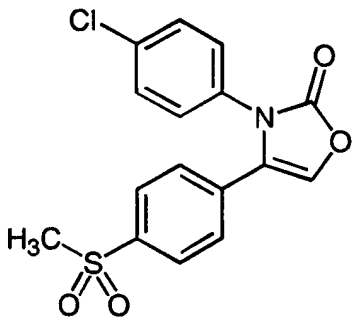
N-[[4-(5-methyl-3-phenylisoxazol-4yl]phenyl]sulfonyl]propanamide;

C8)



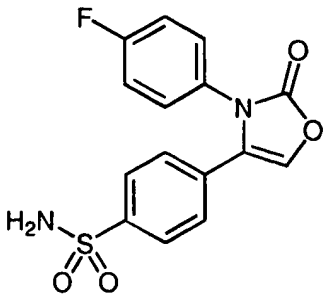
4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide;

C9)



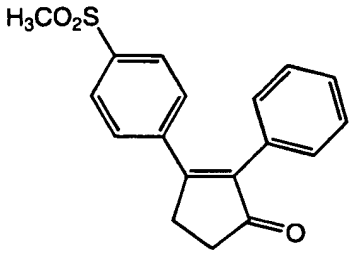
3-(4-chlorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone;

C10)



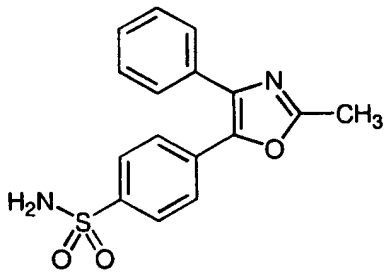
4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide;

C11)



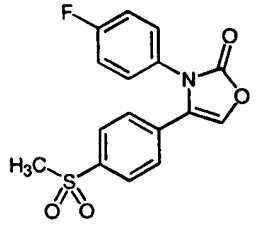
3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one;

C12)



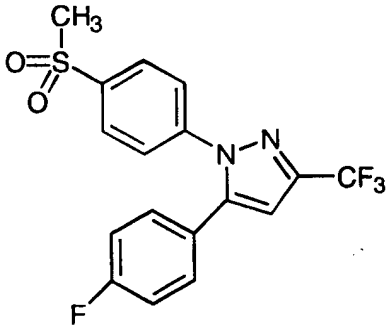
4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide;

C13)



3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone;

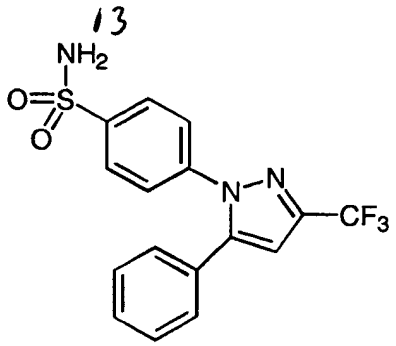
C14)



5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

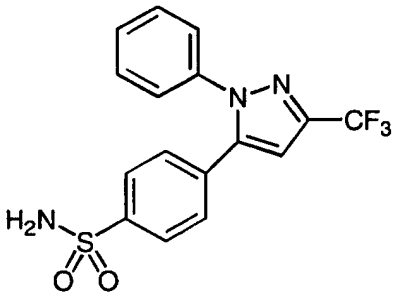
C15)

13



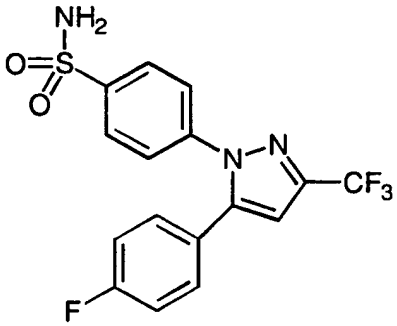
4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;

C16)



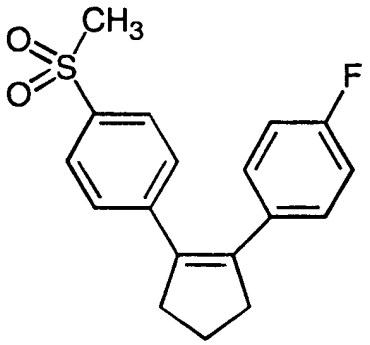
4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

C17)



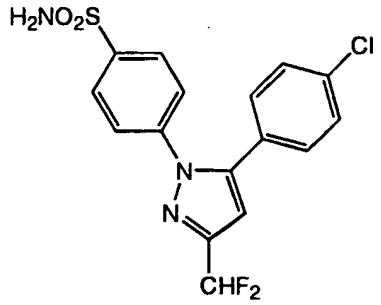
4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

C18)



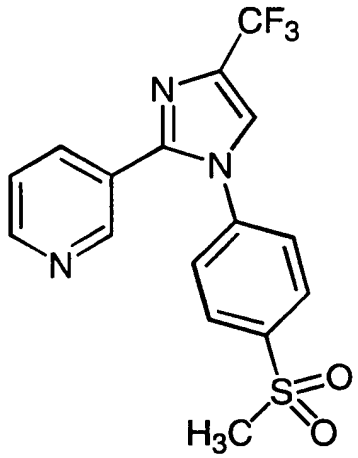
1-fluoro-4-[2-[4-(methylsulfonyl)phenyl]cyclopenten-1-yl]benzene;

C19)



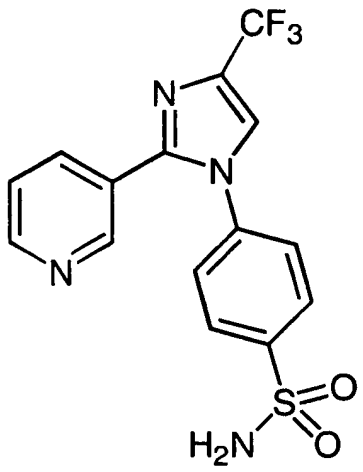
4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

C20)



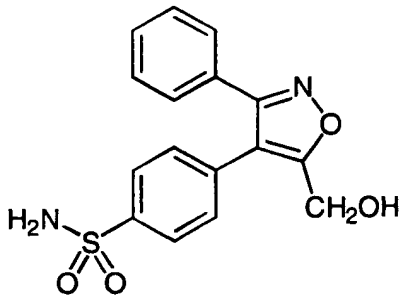
3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

C21)



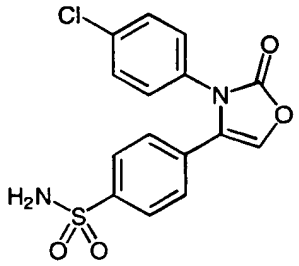
4-[2-(3-pyridinyll)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

C22)



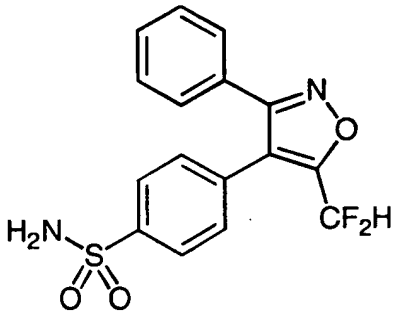
4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide;

C23)



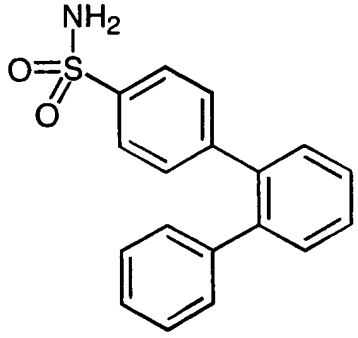
4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide;

C24)



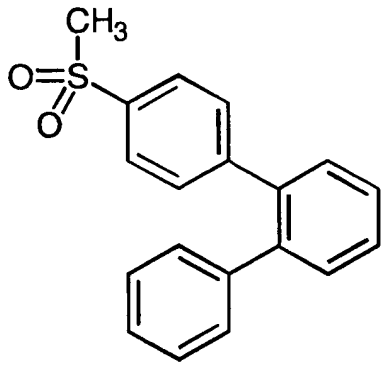
4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide;

C25)



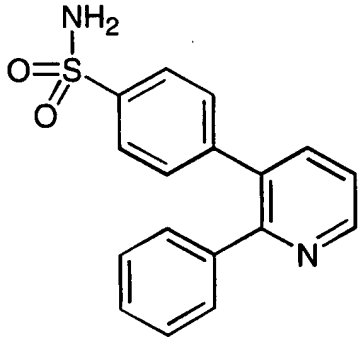
[1,1':2',1"-terphenyl]-4-sulfonamide;

C26)



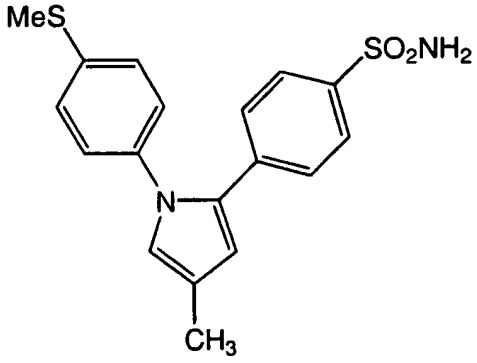
4-(methylsulfonyl)-1,1',2],1"-terphenyl;

C27)



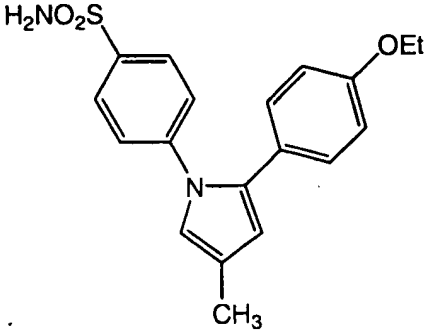
4-(2-phenyl-3-pyridinyl)benzenesulfonamide;

C28)



;

C29)



; and

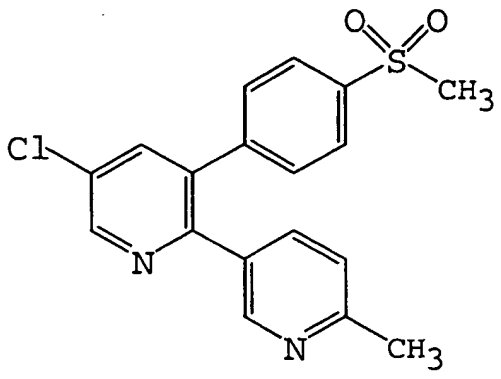
C30) 2-(6-methylpyrid-3-yl)-3-(4-methylsulfinylphenyl)-5-chloropyridine.

Additional specific compounds of particular interest within Formula I include each of the compounds and pharmaceutically-acceptable salts thereof as follows:

4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide,

4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone,

2-(6-methylpyrid-3-yl)-3-(4-methylsulfinylphenyl)-5-chloropyridine:



4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide,

4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone,

4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide,

4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide,

5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine,

2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one,

4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone,

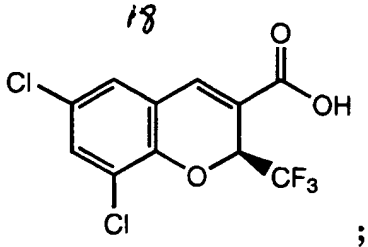
4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide, and

N-[[4-(5-methyl-3-phenylisoxazol-4-yl]phenyl]sulfonyl]propanamide.

Other selective cyclooxygenease-2 inhibiting agents useful in the present invention include compounds such as:

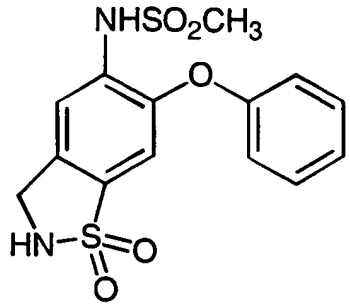
C30)

18



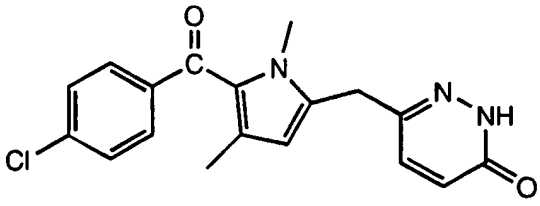
;

C31)



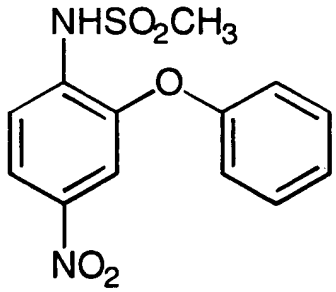
;

C32)



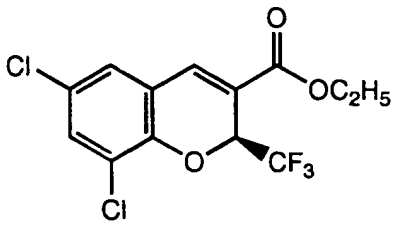
6-[[5-(4-chlorobenzoyl)-1,4—dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone;

C33)

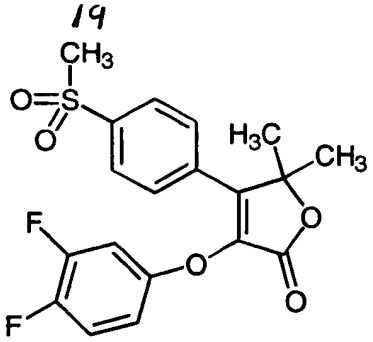


N-(4-nitro-2-phenoxyphenyl)methanesulfonamide;

C34)

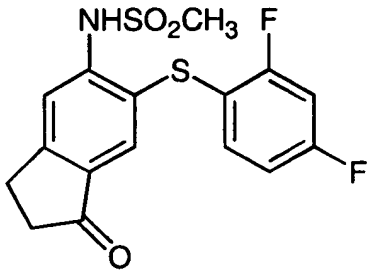


C35)



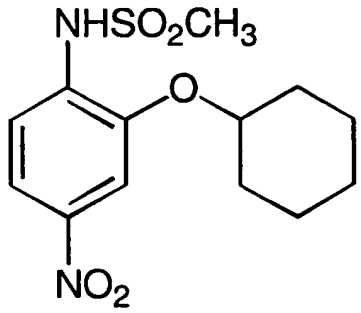
3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone;

C36)



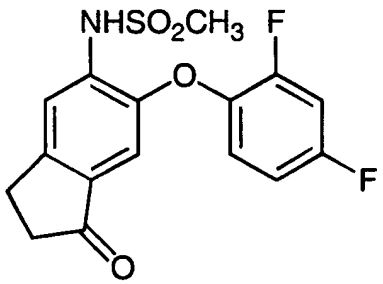
N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide;

C37)



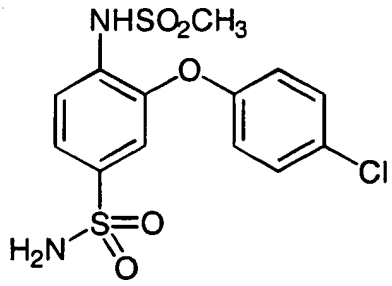
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide;

C38)



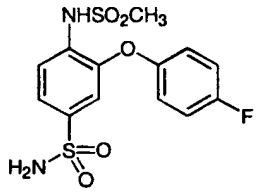
N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide;

C39)



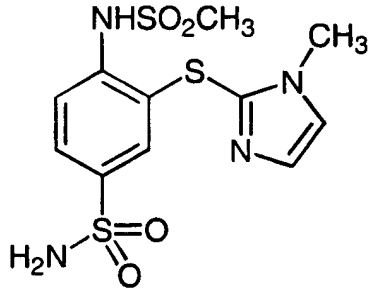
3-(4-chlorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide;

C40)



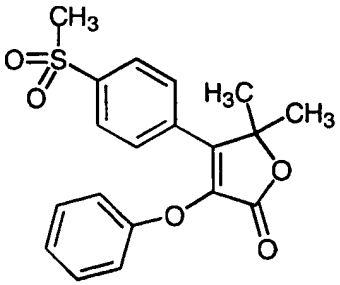
3-(4-fluorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide;

C41)



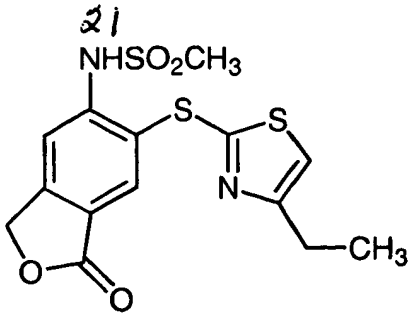
3-[(1-methyl-1H-imidazol-2-yl)thio]-4 [(methylsulfonyl) amino]benzenesulfonamide;

C42)



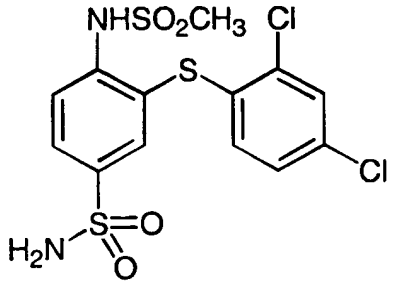
5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone;

C43)



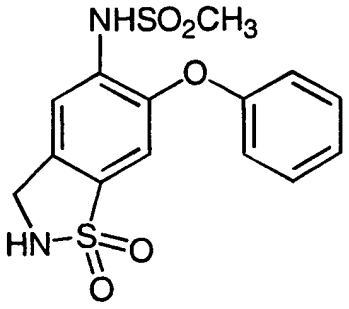
N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide;

C44)



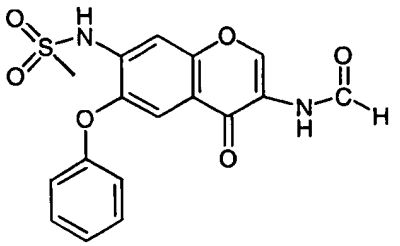
3-[(2,4-dichlorophenyl)thio]-4-[(methylsulfonyl)amino]benzenesulfonamide;

C45)



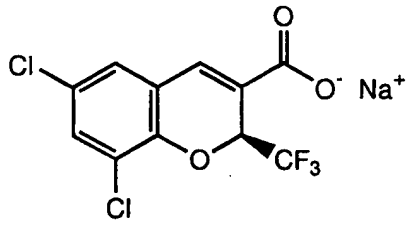
N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide;

C46)



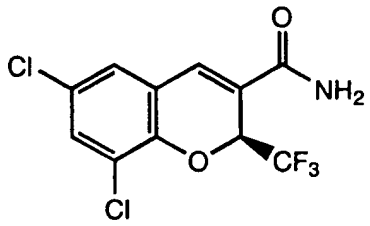
N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide;

C47)



; and

C48)



The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH_2-) radical. Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, *tert*-butyl, pentyl, iso-amyl, hexyl and the like. The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The term "alkynyl" denotes linear or branched radicals having two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about ten carbon atoms. Most preferred are lower alkynyl radicals having two to about six carbon atoms. Examples of such radicals include propargyl, butynyl, and the like. The terms "alkenyl", "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. The term "cycloalkyl" embraces saturated carbocyclic radicals having

three to twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "cycloalkenyl" embraces partially unsaturated carbocyclic radicals having three to twelve carbon atoms. More preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having four to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl and cyclohexenyl. The term "halo" means halogens such as fluorine, chlorine, bromine or iodine. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. The terms "alkoxy" and "alkyloxy" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy. The term "alkoxyalkyl" embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy,

trifluoroethoxy, fluoroethoxy and fluoropropoxy. The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Aryl moieties may also be substituted at a substitutable position with one or more substituents selected independently from alkyl, alkoxyalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkoxy, aralkoxy, hydroxyl, amino, halo, nitro, alkylamino, acyl, cyano, carboxy, aminocarbonyl, alkoxycarbonyl and aralkoxycarbonyl. The term "heterocyclo" embraces saturated, partially unsaturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclo radicals include saturated 3 to 6-membered heteromonocylic group containing 1 to 4 nitrogen atoms (e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. morpholinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl, etc.). Examples of partially unsaturated heterocyclo radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. The term "heteroaryl" embraces unsaturated heterocyclo radicals. Examples of unsaturated heterocyclo radicals, also termed "heteroaryl" radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed heterocyclo group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; unsaturated condensed heterocyclo group

containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. benzoxazolyl, benzoxadiazolyl, etc.); unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.; unsaturated condensed heterocyclo group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl, etc.) and the like. The term also embraces radicals where heterocyclo radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclo group" may have 1 to 3 substituents such as alkyl, hydroxyl, halo, alkoxy, oxo, amino and alkylamino. The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio. The term "alkylthioalkyl" embraces radicals containing an alkylthio radical attached through the divalent sulfur atom to an alkyl radical of one to about ten carbon atoms. More preferred alkylthioalkyl radicals are "lower alkylthioalkyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthioalkyl radicals include methylthiomethyl. The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl. The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkylsulfonyl radicals. The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" denote NH_2O_2S-. The term "acyl" denotes a radical provided by the residue after

removal of hydroxyl from an organic acid. Examples of such acyl radicals include alkanoyl and aroyl radicals. Examples of such lower alkanoyl radicals include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, trifluoroacetyl. The term "carbonyl" or "oxo" whether used alone or with other terms, such as "alkoxycarbonyl", denotes -(C=O)-. The term carbonyl is also intended to encompass a hydrated carbonyl group $-C(OH)_2-$. The term "aroyl" embraces aryl radicals with a carbonyl radical as defined above. Examples of aroyl include benzoyl, naphthoyl, and the like and the aryl in said aroyl may be additionally substituted. The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2H$. The term "carboxyalkyl" embraces alkyl radicals substituted with a carboxy radical. More preferred are "lower carboxyalkyl" which embrace lower alkyl radicals as defined above, and may be additionally substituted on the alkyl radical with halo. Examples of such lower carboxyalkyl radicals include carboxymethyl, carboxyethyl and carboxypropyl. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. More preferred are "lower alkoxycarbonyl" radicals with alkyl portions having 1 to 6 carbons. Examples of such lower alkoxycarbonyl (ester) radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl. The terms "alkylcarbonyl", "arylcarbonyl" and "aralkylcarbonyl" include radicals having alkyl, aryl and aralkyl radicals, as defined above, attached via an oxygen atom to a carbonyl radical. Examples of such radicals include substituted or unsubstituted methylcarbonyl, ethylcarbonyl, phenylcarbonyl and benzylcarbonyl. The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable. The term "heterocycloalkyl" embraces saturated and partially unsaturated heterocyclo-substituted alkyl radicals, such as pyrrolidinylmethyl, and heteroaryl-substituted alkyl radicals, such as pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl, and quinolylethyl. The heteroaryl in said heteroaralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The term "aralkoxy" embraces aralkyl radicals attached through an

oxygen atom to other radicals. The term "aralkoxyalkyl" embraces aralkoxy radicals attached through an oxygen atom to an alkyl radical. The term "aralkylthio" embraces aralkyl radicals attached to a sulfur atom. The term "aralkylthioalkyl" embraces aralkylthio radicals attached through a sulfur atom to an alkyl radical. The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. More preferred are "lower aminoalkyl" radicals. Examples of such radicals include aminomethyl, aminoethyl, and the like. The term "alkylamino" denotes amino groups which have been substituted with one or two alkyl radicals. Preferred are "lower N-alkylamino" radicals having alkyl portions having 1 to 6 carbon atoms. Suitable lower alkylamino may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like. The term "arylamino" denotes amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical. The term "aralkylamino" embraces aralkyl radicals attached through an nitrogen atom to other radicals. The terms "N-arylaminoalkyl" and "N-aryl-N-alkyl-aminoalkyl" denote amino groups which have been substituted with one aryl radical or one aryl and one alkyl radical, respectively, and having the amino group attached to an alkyl radical. Examples of such radicals include N-phenylaminomethyl and N-phenyl-N-methylaminomethyl. The term "aminocarbonyl" denotes an amide group of the formula $-C(=O)NH_2$. The term "alkylaminocarbonyl" denotes an aminocarbonyl group which has been substituted with one or two alkyl radicals on the amino nitrogen atom. Preferred are "N-alkylaminocarbonyl" "N,N-dialkylaminocarbonyl" radicals. More preferred are "lower N-alkylaminocarbonyl" "lower N,N-dialkylaminocarbonyl" radicals with lower alkyl portions as defined above. The term "alkylaminoalkyl" embraces radicals having one or more alkyl radicals attached to an aminoalkyl radical. The term "aryloxyalkyl" embraces radicals having an aryl radical attached to an alkyl radical through a divalent oxygen atom. The term "arylthioalkyl" embraces radicals having an aryl radical attached to an alkyl radical through a divalent sulfur atom.

Suitable pharmaceutically-acceptable base addition salts of compounds of the present invention include metallic ion salts and organic ion salts. More preferred metallic ion salts include, but are not limited to appropriate alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts

and other physiological acceptable metal ions. Such salts can be made from the ions of aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines and quaternary ammonium salts, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of the above salts can be prepared by those skilled in the art by conventional means from the corresponding compound of the present invention.

Also included in the combination of the invention are the isomeric forms and tautomers of the described compounds and the pharmaceutically-acceptable salts thereof. Illustrative pharmaceutically acceptable salts are prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, b-hydroxybutyric, galactaric and galacturonic acids.

The term "cyclooxygenase-2 inhibitor" or "COX-2 inhibitor" or "cyclooxygenase-2 inhibiting agent" or "COX-2 inhibiting agent" embraces compounds that selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. In one embodiment, the compounds have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and in another embodiment have a selectivity ratio of at least 100. Such selectivity ratios may indicate an ability to reduce the incidence of common NSAID-induced side effects.

Nonlimiting examples of cyclooxygenase-2 inhibitors that may be used in the present invention are identified in Table 1 below.

Table 1. Some Cyclooxygenase-2 Inhibitors

Compound	Trade Name	Reference	Dosage
6-chloro-4-hydroxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide, 1,1-dioxide	lornoxicam; Safem®	CAS No. 70374-39-9	
1,5-Diphenyl-3-substituted pyrazoles		WO 97/13755	
	radicicol	WO 96/25928; Kwon et al (Cancer Res(1992) 52 6296)	
	GB-02283745		
	TP-72	Cancer Res. 1998 58 4 717 -723	
1-(4-chlorobenzoyl)-3-[4-(4-fluorophenyl)thiazol-2-ylmethyl]-5-methoxy-2-methy lindole	A-183827.0		
	GR-253035	CAS Registry No. 215522-99-9	
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide; Benzenesulfonamide, 4-(4-cyclohexyl-2-methyl-5-oxazolyl)-2-fluoro-	JTE-522	CAS Registry Number: 180200-68-4; JP 09052882	

Compound	Trade Name	Reference	Dosage
5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine			
2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one			
5-[4-(methylsulfonyl)-phenyl]-6-phenyl-thiazolo[3,2-b][1,2,4]triazole	L-768277	CAS Registry No. 180696-49-5	
	L-783003	CAS Registry No. 215435-69-1	
4-(4-(methyl-sulfonyl)phenyl]-3-phenyl-2(5H)-furanone;	MK-966; Vioxx®; rofecoxib	US 5968974	12.5-100 mg po
indomethacin-derived indolalkanoic acid		WO 96/37467-9	200 mg/kg/day
1-Methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene		WO 95/30656; WO 95/30652; WO 96/38418; WO 96/38442	
4,4-dimethyl-2-phenyl-3-[4-(methylsulfonyl)phenyl]cyclo butenone			
2-(4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole		EP 799823	
N-[5-(4-fluoro)phenoxy]thiophene-2-	RWJ-63556		

Compound	Trade Name	Reference	Dosage
methanesulfonamide			
5(E)-(3,5-di-tert-butyl-4-hydroxy)benzylidene-2-ethyl-1,2-isothiazolidine-1,1-dioxide	S-2474	EP 595546	
3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one	T-614	DE 3834204	
Benzenesulfonamide, 4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)-	celecoxib; Celebrex®	US 5466823	
Benzenesulfonamide, 4-(5-methyl-3-phenyl-4-isoxazolyl)-	valdecoxib	CAS Registry Number: 181695-72-7;	
Propanamide, N-[[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl]-	parecoxib	CAS Registry Number: 198470-84-7; US 5932598	
	meloxicam	US 4233299	15-30 mg/day
	nimesulide	US 3840597	
1,5-Diphenyl-3-substituted pyrazoles		WO 97/13755	
	radicicol	WO 96/25928. Kwon et al (Cancer Res(1992) 52 6296)	
	TP-72	Cancer Res	

Compound	Trade Name	Reference	Dosage
		1998 58 4 717 -723	
1-(4-chlorobenzoyl)-3-[4-(4-fluoro-phenyl)thiazol-2-ylmethyl]-5-methoxy-2-methy lindole	A-183827.0		
	GR-253035		
5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)-pyridine			
2-(3,5-difluoro-phenyl)-3-4-(methylsulfonyl)-phenyl)-2-cyclopenten-1-one			
CS 502	Sankyo		
2-(6-methylpyrid-3-yl)-3-(4-methylsulfinylphenyl)-5-chloropyridine	MK-663; L-791456	WO 98/03484; Bioorg. Med. Chem. Lett. 1998, 8, 2777-2782	

The following individual references listed in Table No. 2 below, each hereby incorporated by reference, describe various cyclooxygenase-2 inhibitors suitable for use in the present invention described herein, and processes for their manufacture.

5

Table No. 2. Some Cyclooxygenase-2 Inhibitor References

WO 99/30721	WO 99/30729	US 5760068	WO 98/15528
WO 99/25695	WO 99/24404	WO 99/23087	FR 27/71005
EP 921119	FR 27/70131	WO 99/18960	WO 99/15505
WO 99/15503	WO 99/14205	WO 99/14195	WO 99/14194
WO 99/13799	GB 23/30833	US 5859036	WO 99/12930

WO 99/11605	WO 99/10332	WO 99/10331	WO 99/09988
US 5869524	WO 99/05104	US 5859257	WO 98/47890
WO 98/47871	US 5830911	US 5824699	WO 98/45294
WO 98/43966	WO 98/41511	WO 98/41864	WO 98/41516
WO 98/37235	EP 86/3134	JP 10/175861	US 5776967
WO 98/29382	WO 98/25896	ZA 97/04806	EP 84/6,689
WO 98/21195	GB 23/19772	WO 98/11080	WO 98/06715
WO 98/06708	WO 98/07425	WO 98/04527	WO 98/03484
FR 27/51966	WO 97/38986	WO 97/46524	WO 97/44027
WO 97/34882	US 5681842	WO 97/37984	US 5686460
WO 97/36863	WO 97/40012	WO 97/36497	WO 97/29776
WO 97/29775	WO 97/29774	WO 97/28121	WO 97/28120
WO 97/27181	WO 95/11883	WO 97/14691	WO 97/13755
WO 97/13755	CA 21/80624	WO 97/11701	WO 96/41645
WO 96/41626	WO 96/41625	WO 96/38418	WO 96/37467
WO 96/37469	WO 96/36623	WO 96/36617	WO 96/31509
WO 96/25405	WO 96/24584	WO 96/23786	WO 96/19469
WO 96/16934	WO 96/13483	WO 96/03385	US 5510368
WO 96/09304	WO 96/06840	WO 96/06840	WO 96/03387
WO 95/21817	GB 22/83745	WO 94/27980	WO 94/26731
WO 94/20480	WO 94/13635	FR 27/70,131	US 5859036
WO 99/01131	WO 99/01455	WO 99/01452	WO 99/01130
WO 98/57966	WO 98/53814	WO 98/53818	WO 98/53817
WO 98/47890	US 5830911	US 5776967	WO 98/22101
DE 19/753463	WO 98/21195	WO 98/16227	US 5733909
WO 98/05639	WO 97/44028	WO 97/44027	WO 97/40012
WO 97/38986	US 5677318	WO 97/34882	WO 97/16435
WO 97/03678	WO 97/03667	WO 96/36623	WO 96/31509
WO 96/25928	WO 96/06840	WO 96/21667	WO 96/19469
US 5510368	WO 96/09304	GB 22/83745	WO 96/03392
WO 94/25431	WO 94/20480	WO 94/13635	JP 09052882

GB 22/94879	WO 95/15316	WO 95/15315	WO 96/03388
WO 96/24585	US 5344991	WO 95/00501	US 5968974
US 5945539	US 5994381		

The celecoxib used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,466,823.

The valdecoxib used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,633,272.

The parecoxib used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,932,598.

The rofecoxib used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,968,974.

The Japan Tobacco JTE-522 used in the therapeutic combinations of the present invention can be prepared in the manner set forth in JP 90/52,882.

The MK-663 used in the therapeutic combination of the present invention can be prepared in the manner set forth in WO document WO 98/03484.

As used herein, the terms "tumor necrosis factor receptor" or "TNFR" refer to proteins having amino acid sequences which are substantially similar to the native mammalian tumor necrosis factor receptor or tumor necrosis factor binding protein amino acid sequences, and which are capable of binding tumor necrosis factor molecules and inhibiting tumor necrosis factor from binding to cell membrane bound tumor necrosis factor receptor. Two distinct types of tumor necrosis factor receptor are known to exist: Type I tumor necrosis factor receptor (TNFRI) and Type II tumor necrosis factor receptor (TNFRII). The mature full-length human TNFRI is a glycoprotein having a molecular weight of about 75-80 kilodaltons (kDa). The mature full-length human TNFRII is a glycoprotein having a molecular weight of about 55-60 kilodaltons (kDa). The preferred tumor necrosis factor receptors of the present invention are soluble forms of TNFRI and TNFRII, as well as soluble tumor necrosis factor binding proteins. Soluble tumor necrosis factor receptor molecules include, for example, analogs or subunits of native proteins having at least 20 amino acids and which exhibit at least some biological activity in common with TNFRI, TNFRII or tumor necrosis factor binding proteins. Soluble tumor necrosis factor receptor

constructs are devoid of a transmembrane region (and are secreted from the cell) but retain the ability to bind tumor necrosis factor. Various bioequivalent protein and amino acid analogs have an amino acid sequence corresponding to all or part of the extracellular region of a native tumor necrosis factor receptor, for example, huTNFRI DELTA 235, huTNFRI DELTA 185 and huTNFRI DELTA 163, and which are biologically active in that they bind to tumor necrosis factor ligand. Equivalent soluble tumor necrosis factor receptors include polypeptides which vary from these sequences by one or more substitutions, deletions, or additions, and which retain the ability to bind tumor necrosis factor or inhibit tumor necrosis factor signal transduction activity via cell surface bound tumor necrosis factor receptor proteins.

The term "TNF antagonist" or "tumor necrosis factor antagonist" or "TNF antagonizing agent" or tumor necrosis factor antagonizing agent" refers to, for example, soluble tumor necrosis factor receptor and tumor necrosis factor binding proteins that bind to tumor necrosis factor and prevent tumor necrosis factor from binding to cell membrane bound tumor necrosis factor receptors. Such proteins competitively bind to cell surface receptors or intracellular tumor necrosis factor recognition sites displacing tumor necrosis factor or preventing tumor necrosis factor from binding to or interacting with the cells, therefore suppressing the biological activities caused by tumor necrosis factor. Tumor necrosis factor antagonizing agents that can be used in the present invention include, but not limited to those described in U.S. Patent No. 5,795,967, hereby incorporated by reference. Other examples of tumor necrosis factor antagonists that may be used in the present invention are identified in Table 3 below.

Table 3. Tumor Necrosis Factor Antagonizing Agents

Compound	**Trade Name**	**Reference**	**Dosage**
	etanercept; ENBREL®	Immunex Corp; CAS Registry Number: 185243-69-0; US 5,605,690;	

Compound	Trade Name	Reference	Dosage
		WO 91/03553	
Undecanoic acid, 2-[(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)methylene]-		CAS Registry Number: 136164-66-4; EP-00419905	
	lenercept; RO-45-2081	CAS Registry Number: 156679-34-4; EP-00417563	
	BB-2275	British Biotech plc; CAS Registry No. 166798-78-3	
	PCM-4	Omega Phaem Inc.	
	SH-636	Schering AG	
	onercept	Amgen Inc.	
	TBP-1	Serono SA; EP-00398327	
	solimastat; BB-3644	British Biotech, plc; WO-09633161	
	MDL-201112;	Hoechst Marion Roussel, Inc.; CAS Registry Number: 142130-73-2 Cyclopentanol, 3-(6-amino-9H-purin-9-yl)-, (1R-cis)-	
	vinigrol	US 5,306,732 CAS Registry No. 111025-83-3	

Compound	Trade Name	Reference	Dosage
	AGT-1	Advanced Biotherapy Concepts, Inc.	
	D-609	Tanabe Research Laboratories; CAS Registry Number: 83373-60-8 Carbonodithioic acid, O-(octahydro-4,7-methano-1H-inden-5-yl) ester, potassium salt	
Pyrrolidinone, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-	rolipram	Schering AG CAS Registry Number: 61413-54-5 2-	
	CytoTAb®	Protherics Molecular Design Ltd	
	Infliximab; Avakine®; Remicade®	Centocor, Inc.; CAS Registry Number: 170277-31-3 Immunoglobulin G (human-mouse monoclonal cA2 heavy chain anti-human tumor necrosis factor), disulfide with human-mouse monoclonal cA2 light	

Compound	Trade Name	Reference	Dosage
		chain, dimer; WO-09216553	

In one embodiment, the tumor necrosis factor antagonist that may be used in the present invention is etanercept (ENBREL®; Immunex Corp), or its biologically active equivalent. ENBREL® is described in U.S. Patent No. 5,605,690 and is hereby incorporated by reference. ENBREL® is a recombinant version of the soluble p75 Tumor Necrosis Factor receptor (TNFR) linked to the Fc portion of human IgG1. It inhibits tumor necrosis factor biological activity by acting as a competitive inhibitor to the binding of tumor necrosis factor to its cell receptors. For treatment of arthritis or inflammation, tumor necrosis factor is administered in systemic amounts ranging from about 0.1 mg/kg/week to about 100 mg/kg/week. In one embodiments of the present invention, tumor necrosis factor antagonist is administered in amounts ranging from about 0.5 mg/kg/week to about 50 mg/kg/week. For local intra-articular administration, dosages preferably range from about 0.01 mg/kg to about 1.0 mg/kg per injection. In another embodiment of the present invention the adult dose of ENBREL® (entanercept) is 25 mg twice a day, as a subcutaneous injection.

"Biologically active," as used throughout the specification as a characteristic of tumor necrosis factor receptor antagonizing agent, means, for example, that a particular molecule shares sufficient amino acid sequence similarity with the embodiments of the present invention disclosed herein to be capable of binding detectable quantities of tumor necrosis factor receptor, transmitting a tumor necrosis factor stimulus to a cell, for example, as a component of a hybrid receptor construct, or cross-reacting with anti-tumor necrosis factor receptor antibodies raised against tumor necrosis factor receptor from natural (i.e., nonrecombinant) sources. In one embodiment of the present invention, the biologically active tumor necrosis factor receptor antagonizing agent within the scope of the present invention are capable of binding greater than 0.1 nmoles tumor necrosis factor per nmole receptor, and in another embodiment, are capable of binding greater than 0.5 nmole tumor necrosis factor per nmole receptor in standard binding assays (see U.S. Patent No. 5.605,690).

The phrase "combination therapy" (or "co-therapy") embraces the administration of a cyclooxygenase-2 inhibiting agent and a tumor necrosis factor antagonizing agent as part of a specific treatment regimen intended to provide a beneficial effect from the co-action of these therapeutic agents. The beneficial effect of the combination includes, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents. Administration of these therapeutic agents in combination typically is carried out over a defined time period (usually minutes, hours, days or weeks depending upon the combination selected). "Combination therapy" generally is not intended to encompass the administration of two or more of these therapeutic agents as part of separate monotherapy regimens that incidentally and arbitrarily result in the combinations of the present invention. "Combination therapy" is intended to embrace administration of these therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single capsule or intravenous injection having a fixed ratio of each therapeutic agent or in multiple, single capsules or intravenous injections for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally. Alternatively, for example, all therapeutic agents may be administered orally or all therapeutic agents may be administered by intravenous injection. The sequence in which the therapeutic agents are administered is not narrowly critical.

The term "pharmaceutically acceptable" is used adjectivally herein to mean that the modified noun is appropriate for use in a pharmaceutical product. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Exemplary

ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include without limitation hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

The term "treatment" refers to any process, action, application, therapy, or the like, wherein a mammal, including a human, is subject to medical aid with the object of improving the mammal's condition, directly or indirectly.

The phrase "therapeutically-effective" is intended to qualify the amount of each agent that will achieve the goal of improvement in arthritic disease severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies.

A "therapeutic effect" relieves to some extent one or more of the symptoms of an arthritic or inflammatory disorder. In reference to the treatment of rheumatoid arthritis, a therapeutic effect refers to one or more of the following: 1) relieving or reducing to some extent one or more of the symptoms associated with the disorder, 2) relieving or reducing to some extent gastrointestinal upset, 3) relieving or reducing to some extent mucosal ulcerations, 4) relieving or reducing to some extent renal impairment, 5) relieving or reducing to some extent pulmonary toxicity, and/or 6) relieving or reducing the side effects associated with the administration of other antiarthritic agents, such as disease modifying antirheumatic drugs.

Dosage levels of cyclooxygenase-2 inhibitors on the order of about 0.1 mg to about 10,000 mg of the active ingredient compound are useful in the treatment of the above conditions, with preferred levels of about 0.1 mg to about 1,000 mg. The amount of active ingredient that may be combined with other agents to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

For therapeutic use, purified soluble tumor necrosis factor receptor antagonizing agent is administered to a patient, preferably a human, for treatment of an inflammation disorder, for example arthritis. Thus, for example, soluble tumor necrosis factor receptor antagonist compositions can be administered by parental administration, for example, intravenous injection, subcutaneous injection, intramuscular injection, or intramedullary injection. Other routes of administration for tumor necrosis factor receptor antagonizing agents include, for example, intra-articular, intraperitoneal or subcutaneous routes by bolus injection, continuous infusion, sustained release from implants, or other suitable techniques. Typically, a soluble tumor necrosis factor receptor therapeutic agent will be administered in the form of a composition comprising purified protein in conjunction with physiologically acceptable carriers, excipients or diluents. Such carriers will be nontoxic to recipients at the dosages and concentrations employed. Ordinarily, the preparation of such compositions entails combining the tumor necrosis factor receptor with buffers, antioxidants such as ascorbic acid, low molecular weight (less than about 10 residues) polypeptides, proteins, amino acids, carbohydrates including glucose, sucrose or dextrins, chelating agents such as EDTA, glutathione and other stabilizers and excipients. Neutral buffered saline or saline mixed with nonspecific serum albumin are exemplary appropriate diluents. Preferably, product is formulated as a lyophilizate using appropriate excipient solutions (e.g., sucrose) as diluents. Appropriate dosages can be determined in trials. In accordance with appropriate industry standards, preservatives may also be added, such as benzyl alcohol. The amount and frequency of administration will depend, of course, on such factors as the nature and severity of the indication being treated, the desired response, the condition of the patient, and so forth.

For treatment of arthritis or an inflammatory disorder, tumor necrosis factor receptor antagonizing agent is administered in systemic amounts ranging from about 0.1 mg/kg/week to about 100 mg/kg/week. In one embodiment of the present invention, tumor necrosis factor receptor antagonizing agent is administered in amounts ranging from about 0.5 mg/kg/week to about 50 mg/kg/week. For local intra-articular administration, dosages preferably range from about 0.01 mg/kg to about 1.0 mg/kg per injection.

It is understood, however, that a specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the severity of the particular disease being treated and form of administration.

Treatment dosages generally may be titrated to optimize safety and efficacy. Typically, dosage-effect relationships from in vitro initially can provide useful guidance on the proper doses for patient administration. Studies in animal models also generally may be used for guidance regarding effective dosages for treatment of rheumatoid arthritis in accordance with the present invention. In terms of treatment protocols, it should be appreciated that the dosage to be administered will depend on several factors, including the particular agent that is administered, the route administered, the condition of the particular patient, etc. It will generally be desirable to administer the cyclooxygenase inhibitor either parenterally, intravenously, or subcutaneously. Other routes of administration are also contemplated, including intranasal and transdermal routes, and by inhalation. When administered, the therapeutic composition for use in this invention is preferably in the form of a pyrogen-free, parenterally-acceptable aqueous solution. The preparation of such a parenterally-acceptable protein solution, having due regard to pH, isotonicity, stability and the like, is within the skill of the art. However, administration by other routes is contemplated where appropriate. Generally speaking, one will desire to administer an amount of the agent that is effective to achieve a serum level commensurate with the concentrations found to be effective in vitro. Thus, where an agent is found to demonstrate in vitro activity at, e.g., 10 μM, one will desire to administer an amount of the drug that is effective to provide about a 10 μM concentration in vivo. Determination of these parameters is well within the skill of the art.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed

as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, polyethylene glycols can be used. Mixtures of solvents and wetting agents such as those discussed above are also useful.

Suppositories for rectal administration of the drugs can be prepared by mixing the drugs with a suitable nonirritating excipient such as cocoa butter, synthetic mono- di- or triglycerides, fatty acids and polyethylene glycols that are sold at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration can include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, a contemplated aromatic sulfone hydroximate inhibitor compound can be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation as can be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents such as sodium citrate, magnesium or calcium carbonate or bicarbonate. Tablets and pills can additionally be prepared with enteric coatings.

For therapeutic purposes, formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions can be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. A contemplated aromatic sulfone hydroximate inhibitor compound can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form varies depending upon the mammalian host treated and the particular mode of administration.

A combination of the present invention can be formulated as a pharmaceutical composition. Such a composition can then be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration can also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

The above considerations regarding effective formulations and administration procedures are well known in the art and are described in standard textbooks. Drug formulations are discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania; 1975, hereby incorporated by reference. Another discussion of drug formulations can be found in Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980, hereby incorporated by reference.

BIOLOGICAL EVALUATION

A combination therapy of a cyclooxygenase-2 inhibitor and a tumor necrosis factor antagonist for the treatment of an arthritic or inflammatory disorder in a mammal can be evaluated as described in the following tests.

Induction and assessment of collagen induced arthritis in mice

Arthritis is induced in 8-12 week old male DBA/1 mice by injection of 50 mg of chick type II collagen (CII) in complete Freunds adjuvant (Sigma) on day 0 at the

base of the tail as previously described [J. Stuart, *Annual Rev. Immunol.*, 2, 199 (1984)]. Compounds are prepared as a suspension in 0.5% methylcellulose (Sigma, St. Louis, MO), 0.025% Tween 20 (Sigma). The cyclooxygenase-2 inhibitors and the tumor necrosis factor antagonist are administered alone or a cyclooxygenase-2 inhibitor and the tumor necrosis factor antagonist in combination. The compounds are administered in non-arthritic animals by gavage in a volume of 0.1 ml beginning on day 20 post collagen injection and continuing daily until final evaluation on day 55. Animals are boosted on day 21 with 50 mg of collagen (CII) in incomplete Freunds adjuvant. The animals are subsequently evaluated several times each week for incidence and severity of arthritis until approximately day 56. Any animal with paw redness or swelling is counted as arthritic. Scoring of severity is carried out using a score of 0-3 for each paw (maximal score of 12/mouse) as previously described [P. Wooley, *et al.*, *Trans. Proc.*, 15, 180 (1983)]. The animals are measured for incidence of arthritis and severity in the animals where arthritis is observed. The incidence of arthritis is determined at a gross level by observing the swelling or redness in the paw or digits. Severity is measured with the following guidelines. Briefly, animals displaying four normal paws, i.e., no redness or swelling are scored 0. Any redness or swelling of digits or the paw is scored as 1. Gross swelling of the whole paw or deformity is scored as 2. Ankylosis of joints is scored as 3.

Histological Examination of Paws

In order to verify the gross determination of a non-arthritic animal, a histological examination is performed. Paws from animals sacrificed at the end of the experiment were removed, fixed and decalcified as previously described [R. Jonsson, *J. Immunol. Methods*, **88**, 109 (1986)]. Samples are paraffin embedded, sectioned, and stained with hematoxylin and eosin by standard methods. Stained sections are examined for cellular infiltrates, synovial hyperplasia, and bone and cartilage erosion.

Rat Carrageenan Foot Pad Edema Test

The carrageenan foot edema test is performed with materials, reagents and procedures essentially as described by Winter et al., (Proc. Soc. Exp. Biol. Med., 111, 544 (1962)). Male Sprague-Dawley rats are selected in each group so that the average body weight is as close as possible. Rats are fasted with free access to water for over

sixteen hours prior to the test. The rats are dosed orally (1 mL) with compounds suspended in vehicle containing 0.5% methylcellulose and 0.025% surfactant, or with vehicle alone. One hour later a subplantar injection of 0.1 mL of 1% solution of carrageenan/sterile 0.9% saline is administered and the volume of the injected foot is measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot is again measured. The average foot swelling in a group of drug-treated animals is compared with that of a group of placebo-treated animals and the percentage inhibition of edema is determined (Otterness and Bliven, Laboratory Models for Testing NSAIDs, in Non-steroidal Anti-Inflammatory Drugs, (J. Lombardino, ed. 1985)).

Rat Carrageenan-induced Analgesia Test

The analgesia test using rat carrageenan is performed with materials, reagents and procedures essentially as described by Hargreaves, et al., (Pain, 32, 77 (1988)). Male Sprague-Dawley rats are treated as previously described for the Carrageenan Foot Pad Edema test. Three hours after the injection of the carrageenan, the rats are placed in a special plexiglass container with a transparent floor having a high intensity lamp as a radiant heat source, positionable under the floor. After an initial twenty minute period, thermal stimulation is begun on either the injected foot or on the contralateral uninjected foot. A photoelectric cell turns off the lamp and timer when light is interrupted by paw withdrawal. The time until the rat withdraws its foot is then measured. The withdrawal latency in seconds is determined for the control and drug-treated groups, and percent inhibition of the hyperalgesic foot withdrawal determined.

Besides being useful for human treatment, the method, combinations, agents and compositions of the present invention are also useful for treatment of mammals, including, but not limited to, horses, dogs, cats, rats, mice, sheep, pigs, etc.

The present invention further includes kits comprising a cyclooxygenase-2 inhibitor and a tumor necrosis factor antagonist.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

What is claimed is:

1. A method for treating an inflammatory disorder in a mammal in need thereof, comprising administering to the mammal a tumor necrosis factor antagonizing agent and a selective cyclooxygenase-2 inhibiting agent, wherein the tumor necrosis factor antagonizing agent and the selective cyclooxygenase-2 inhibiting agent together comprise an inflammatory disorder effective amount of the agents.

2. The method of claim 1 wherein the tumor necrosis factor antagonizing agent is a protein.

3. The method of claim 2 wherein the protein competitively binds to a cell surface tumor necrosis factor receptor.

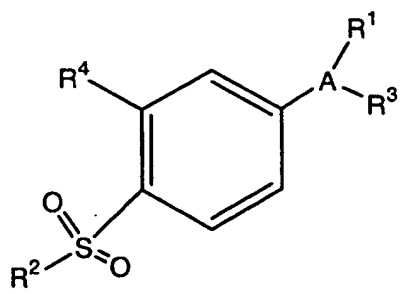
4. The method of claim 2 wherein the protein competitively binds to an intracellular tumor necrosis factor receptor.

5. The method of claim 2 wherein the tumor necrosis factor antagonizing agent is etanercept.

6. The method of claim 1 wherein the tumor necrosis factor antagonizing agent is selected from the group consisting of 2-[(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)methylene]-undecanoic acid; lenercept; etanercept; BB-2275; PCM-4; SH-636; onercept; vinigrol; TBP-1; solimastat; MDL-201112; AGT-1; D-609; 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-pyrrolidinone; CytoTAb®; and Infliximab.

7. The method of claim 1 wherein the selective cyclooxygenase-2 inhibiting agent is selected from compounds of Formula 1:

49



1.

wherein

A is a 5- or 6-member ring substituent selected from partially unsaturated or unsaturated heterocyclo and carboxcyclic rings, wherein A is optionally substituted with one or more radicals selected from the group consisting of alkyl, halo, oxo, and alkoxy;

R^1 is selected from the group consisting of cyclohexyl, pyridinyl, and phenyl, wherein cyclohexyl, pyridinyl, or phenyl are optionally substituted with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, phenylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio;

R^2 is selected from the group consisting of alkyl and amino;

R^3 is a radical selected from the group consisting of halo, alkyl, alkenyl, alkynyl, aryl, heteroaryl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, phenyl, haloalkyl, heterocyclo, cycloalkenyl, phenylalkyl, heterocyclylalkyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, phenylcarbonyl, phenylalkylcarbonyl, phenylalkenyl, alkoxyalkyl, phenylthioalkyl, phenylyloxyalkyl, alkoxyphenylalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-phenylaminocarbonyl, N-alkyl-N-phenylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-arylkylamino, N-alkyl-N-arylkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-phenylaminoalkyl, N-phenylalkylaminoalkyl, N-alkyl-N-phenylalkylaminoalkyl, N-alkyl-N-phenylaminoalkyl, phenyloxy, phenylalkoxy, phenylthio, phenylalkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-alkyl-N-phenylaminosulfonyl; and

R^4 is selected from the group consisting of hydrido and halo;

or a pharmaceutically-acceptable salt thereof.

8. The method of claim 7 wherein A is selected from the group consisting of thienyl, oxazolyl, furyl, furanone, pyrrolyl, thiazolyl, imidazolyl, benzofuryl, indenyl, benzithienyl, isoxazolyl, pyrazolyl, cyclopentenyl, cyclopentadienyl, benzindazolyl, cyclopentenone, benzopyranopyrazolyl, phenyl, and pyridyl.

9. The method of claim 8 wherein A is substituted with one or more radicals selected from the group consisting of alkyl, halo, oxo, and alkoxy.

10. The method of claim 9 wherein A is substituted with one or more halo radical.

11. The method of claim 10 wherein the halo is choro.

12. The method of claim 9 wherein A is substituted by one or more alkyl radical.

13. The method of claim 12 wherein the alkyl is methyl.

14. The method of claim 9 wherein A is substituted with one or more oxo moiety.

15. The method of claim 9 wherein A is substituted with one or more alkoxy radical.

16. The method of claim 7 wherein R^1 is selected from the group consisting of cyclohexyl, pyridinyl, and phenyl, wherein cyclohexyl, pyridinyl, or phenyl is optionally substituted with one or more radicals selected from C_{1-2} alkyl, C_{1-2} haloalkyl, cyano, carboxyl, C_{1-2} alkoxycarbonyl, hydroxyl, C_{1-2} hydroxyalkyl, C_{1-2} haloalkoxy, amino, C_{1-2} alkylamino, phenylamino, nitro, C_{1-2} alkoxy-C_{1-2}-alkyl, C_{1-2} alkylsulfinyl, C_{1-2} alkoxy, halo, alkoxy, and C_{1-2} alkylthio.

17. The method of claim 7 wherein R^1 is selected from the group consisting of pyridyl, cyclohexyl, and phenyl, wherein pyridyl, cyclohexyl, or phenyl is optionally substituted with one or more radicals selected from the group consisting of alkyl, halo, and alkoxy.

18. The method of claim 17 wherein R^1 is pyridyl.

19. The method of claim 18 wherein pyridyl is substituted with one or more radicals selected from the group consisting of alkyl, halo, and alkoxy.

20. The method of claim 19 wherein the pyridyl is substituted with alkyl.

21. The method of claim 20 wherein alkyl is C_{1-2} alkyl.

22. The method of claim 21 wherein alkyl is methyl.

23. The method of claim 19 wherein the pyridyl is substituted with halo.

24. The method of claim 23 wherein the halo is chloro.

25. The method of claim 17 wherein R^1 is cyclohexyl.

26. The method of claim 25 wherein the cyclohexyl is substituted with one or more radicals selected from the group consisting of alkyl, halo, and alkoxy.

27. The method of claim 25 wherein the cyclohexyl is substituted with alkyl.

28. The method of claim 27 wherein the alkyl is C_{1-2} alkyl.

29. The method of claim 28 wherein the alkyl is methyl.

30. The method of claim 25 wherein the pyridyl is substituted with halo.

31. The method of claim 30 wherein the halo is chloro.

32. The method of claim 17 wherein R^1 is phenyl optionally substituted with one or more radicals selected from the group consisting of alkyl, halo, and alkoxy..

33. The method of claim 32 wherein the phenyl is substituted with one or more radicals selected from the group consisting of alkyl, halo, and alkoxy.

34. The method of claim 33 wherein the phenyl is substituted with alkyl.

35. The method of claim 34 wherein the alkyl is C_{1-2} alkyl.

36. The method of claim 35 wherein the alkyl is methyl.

37. The method of claim 7 wherein R^2 is alkyl or amino.

38. The method of claim 37 wherein the alkyl is C_{1-2} alkyl.

39. The method of claim 38 wherein the alkyl is methyl.

40. The method of claim 7 wherein R^3 is a radical selected from the group consisting of halo, C_{1-2} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, aryl, heteroaryl, oxo, cyano, carboxyl, cyano-C_{1-3}-alkyl, heterocyclyloxy, C_{1-3} alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, phenyl, C_{1-3} haloalkyl, heterocyclo, cycloalkenyl, phenyl-C_{1-3}-alkyl, heterocyclyl-C_{1-3}-alkyl, C_{1-3} alkylthio-C_{1-3}-alkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxycarbonyl, phenylcarbonyl, phenyl-C_{1-3}-alkylcarbonyl, phenyl-C_{2-3}-alkenyl, C_{1-3} alkoxy-C_{1-3}-alkyl, phenylthio-C_{1-3}-alkyl, phenylyloxyalkyl, alkoxyphenylalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonyl-C_{1-3}-alkyl, C_{1-3} alkylaminocarbonyl, N-phenylaminocarbonyl, N-C_{1-3} alkyl-N-phenylaminocarbonyl, C_{1-3} alkylaminocarbonyl-C_{1-3}-alkyl, carboxy-C_{1-3}-alkyl, C_{1-3} alkylamino, N-arylamino, N-arylkylamino, N-C_{1-3} alkyl-N-arylkylamino, N-C_{1-3} alkyl-N-arylamino, amino-C_{1-3}-

alkyl, C_{1-3} alkylaminoalkyl, N-phenylamino-C_{1-3}-alkyl, N-phenyl-C_{1-3}-alkylaminoalkyl, N-C_{1-3} alkyl-N-phenyl-C_{1-3}-alkylamino-C_{1-3}-alkyl, N-C_{1-3} alkyl-N-phenylamino-C_{1-3}-alkyl, phenyloxy, phenylalkoxy, phenylthio, phenyl-C_{1-3}-alkylthio, C_{1-3} alkylsulfinyl, C_{1-3} alkylsulfonyl, aminosulfonyl, C_{1-3} alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-C_{1-3} alkyl-N-phenylaminosulfonyl.

41. The method of claim 40 wherein R^3 is a radical selected from the group consisting of halo, C_{1-2} alkyl, cyano, carboxyl, C_{1-2} alkyloxy, phenyl, C_{1-2} haloalkyl, and C_{1-2} hydroxyalkyl.

42. The method of claim 7 wherein R^4 is hydrido.

43. The method of claim 7 wherein R^4 is halo.

44. The method of claim 43 wherein the halo is fluoro.

45. The method of claim 7 wherein the selective cyclooxygenase-2 inhibiting agent is 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide,

46. The method of claim 7 wherein the selective cyclooxygenase-2 inhibiting agent is 4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone.

47. The method of claim 7 wherein the selective cyclooxygenase-2 inhibiting agent is 2-(6-methylpyrid-3-yl)-3-(4-methylsulfinylphenyl)-5-chloropyridine.

48. The method of claim 7 wherein the selective cyclooxygenase-2 inhibiting agent is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide.

49. The method of claim 7 wherein the selective cyclooxygenase-2 inhibiting agent is 4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone.

50. The method of claim 7 wherein the selective cyclooxygenase-2 inhibiting agent is 4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide.

51. The method of claim 7 wherein the selective cyclooxygenase-2 inhibiting agent is 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide.

52. The method of claim 7 wherein the selective cyclooxygenase-2 inhibiting agent is 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine.

53. The method of claim 7 wherein the selective cyclooxygenase-2 inhibiting agent is 2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one.

54. The method of claim 7 wherein the selective cyclooxygenase-2 inhibiting agent is 4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone.

55. The method of claim 7 wherein the selective cyclooxygenase-2 inhibiting agent is 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide.

56. The method of claim 7 wherein the selective cyclooxygenase-2 inhibiting agent is N-[[4-(5-methyl-3-phenylisoxazol-4-yl]phenyl]sulfonyl]propanamide.

57. The method of claim 1 wherein the agents are administered in a sequential manner.

58. The method of claim 1 wherein the agents are administered in a substantially simultaneous manner.

59. The method of claim 1 wherein the tumor necrosis factor antagonizing agent is administered parentally.

60. The method of claim 59 wherein the parental administration is by intravenous injection, subcutaneous injection, intramuscular injection, or intramedullary injection.

61. The method of claim 1 wherein the cyclooxygenase-2 inhibiting agent and the tumor necrosis factor antagonizing agent are formulated in a single composition.

62. The method of claim 1 wherein the cyclooxygenase-2 inhibiting agent and the tumor necrosis factor antagonizing agent are each provided as a separate component of a kit.

63. The method of claim 1 wherein the inflammatory disorder is selected from the group consisting of rheumatoid arthritis, osteoarthritis, spondylarthropy, ankylosing spondylitis, psoriatic arthritis, reactive arthritis, IBD related arthritis, undifferentiated spondyloarthropathy, Reider's syndrome, systemic lupus erythematosus, Behcet's disease, eosinophilia fasciitis, eosinophila-myalgia syndrome, familial Mediterranean fever, hereditary angioedema, juvenile chronic arthritis, palindromic rheumatism, idiopathic polymyositis, dermatomyositis, inclusion body myositis, systemic sclerosis, atherosclerosis; sarcoidisis, Reynaud's phenomenon, Sjogren's syndrome, Still's disease, systemic rheumatoid vasculitis, vasculitis, Wegener's granulomatosis, Whipple's disease, and xerostomia.

64. The method of claim 63 wherein the inflammatory disorder is selected from the group consisting of rheumatoid arthritis, and osteoarthritis.

65. The method of claim 64 wherein the inflammatory disorder is rheumatoid arthritis.

66. The method of claim 64 wherein the inflammatory disorder is osteoarthritis.

67. A method for treating an inflammatory disorder in a mammal in need thereof, comprising administering to the mammal a tumor necrosis factor antagonizing

agent and a selective cyclooxygenase-2 inhibiting agent, wherein the agents together comprise an inflammatory disorder effective amount of the agents.

68. The method of claim 67 wherein the tumor necrosis factor antagonizing agent is a protein.

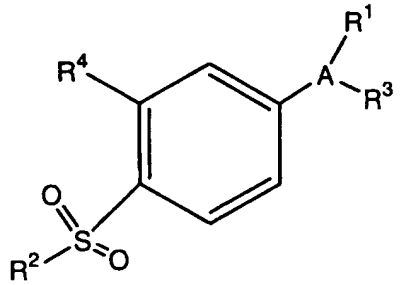
69. The method of claim 68 wherein the protein competitively binds to a cell surface tumor necrosis factor receptor.

70. The method of claim 68 wherein the protein competitively binds to an intracellular tumor necrosis factor receptor.

71. The method of claim 68 wherein the tumor necrosis factor antagonizing agent is etanercept.

72. The method of claim 67 wherein the tumor necrosis factor antagonizing agent is selected from the group consisting of 2-[(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)methylene]-undecanoic acid; etanercept; lenercept; BB-2275; PCM-4; SH-636; onercept; TBP-1; solimastat; MDL-201112; AGT-1; D-609; 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-pyrrolidinone; CytoTAb®; and Infliximab.

73. The method of claim 67 wherein the selective cyclooxygenase-2 inhibiting agent is selected from compounds of Formula 1:



1.

wherein

A is a 5- or 6-member ring substituent selected from partially unsaturated or unsaturated heterocyclo and carboxcyclic rings, wherein A is optionally substituted

with one or more radicals selected from the group consisting of alkyl, halo, oxo, and alkoxy;

R^1 is selected from the group consisting of cyclohexyl, pyridinyl, and phenyl, wherein cyclohexyl, pyridinyl, or phenyl are optionally substituted with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, phenylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio;

R^2 is selected from the group consisting of alkyl and amino;

R^3 is a radical selected from the group consisting of halo, alkyl, alkenyl, alkynyl, aryl, heteroaryl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, phenyl, haloalkyl, heterocyclo, cycloalkenyl, phenylalkyl, heterocyclylalkyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, phenylcarbonyl, phenylalkylcarbonyl, phenylalkenyl, alkoxyalkyl, phenylthioalkyl, phenylyloxyalkyl, alkoxyphenylalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-phenylaminocarbonyl, N-alkyl-N-phenylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-arylkylamino, N-alkyl-N-arylkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-phenylaminoalkyl, N-phenylalkylaminoalkyl, N-alkyl-N-phenylalkylaminoalkyl, N-alkyl-N-phenylaminoalkyl, phenyloxy, phenylalkoxy, phenylthio, phenylalkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-alkyl-N-phenylaminosulfonyl; and

R^4 is selected from the group consisting of hydrido and halo;

or a pharmaceutically-acceptable salt thereof.

74. The method of claim 73 wherein A is selected from the group consisting of thienyl, oxazolyl, furyl, furanone, pyrrolyl, thiazolyl, imidazolyl, benzofuryl, indenyl, benzithienyl, isoxazolyl, pyrazolyl, cyclopentenyl, cyclopentadienyl, benzindazolyl, cyclopentenone, benzopyranopyrazolyl, phenyl, and pyridyl.

75. The method of claim 74 wherein A is substituted with one or more radicals selected from the group consisting of alkyl, halo, oxo, and alkoxy.

76. The method of claim 75 wherein A is substituted with halo.

77. The method of claim 76 wherein the halo is choro.

78. The method of claim 77 wherein A is substituted by alkyl.

79. The method of claim 78 wherein the alkyl is methyl.

80. The method of claim 75 wherein A is substituted with oxo.

81. The method of claim 75 wherein A is substituted with alkoxy.

82. The method of claim 73 wherein R^1 is selected from the group consisting of cyclohexyl, pyridinyl, and phenyl, wherein cyclohexyl, pyridinyl, or phenyl is substituted with one or more radicals selected from C_{1-2} alkyl, C_{1-2} haloalkyl, cyano, carboxyl, C_{1-2} alkoxycarbonyl, hydroxyl, C_{1-2} hydroxyalkyl, C_{1-2} haloalkoxy, amino, C_{1-2} alkylamino, phenylamino, nitro, C_{1-2} alkoxy-C_{1-2}-alkyl, C_{1-2} alkylsulfinyl, C_{1-2} alkoxy, halo, alkoxy, and C_{1-2} alkylthio.

83. The method of claim 73 wherein R^1 is selected from the group consisting of pyridyl, cyclohexyl, and phenyl, wherein pyridyl, cyclohexyl, or phenyl is optionally substituted with one or more radicals selected from the group consisting of alkyl, halo, and alkoxy.

84. The method of claim 83 wherein R^1 is pyridyl.

85. The method of claim 84 wherein pyridyl is substituted with one or more radicals selected from the group consisting of alkyl, halo, and alkoxy.

86. The method of claim 85 wherein the pyridyl is substituted with alkyl.

87. The method of claim 86 wherein alkyl is C_{1-2} alkyl.

88. The method of claim 87 wherein alkyl is methyl.

89. The method of claim 85 wherein the pyridyl is substituted with halo.

90. The method of claim 89 wherein the halo is chloro.

91. The method of claim 83 wherein R^1 is cyclohexyl.

92. The method of claim 91 wherein the cyclohexyl is substituted with one or more radicals selected from the group consisting of alkyl, halo, and alkoxy.

93. The method of claim 91 wherein the cyclohexyl is substituted with alkyl.

94. The method of claim 93 wherein the alkyl is C_{1-2} alkyl.

95. The method of claim 94 wherein the alkyl is methyl.

96. The method of claim 92 wherein the pyridyl is substituted with halo.

97. The method of claim 96 wherein the halo is chloro.

98. The method of claim 83 wherein R^1 is phenyl.

99. The method of claim 98 wherein the phenyl is substituted with one or more radicals selected from the group consisting of alkyl, halo, and alkoxy.

100. The method of claim 99 wherein the phenyl is substituted with alkyl.

101. The method of claim 100 wherein the alkyl is C_{1-2} alkyl.

102. The method of claim 101 wherein the alkyl is methyl.

103. The method of claim 73 wherein R^2 is alkyl or amino.

104. The method of claim 103 wherein the alkyl is C_{1-2} alkyl.

105. The method of claim 104 wherein the alkyl is methyl.

106. The method of claim 73 wherein R^3 is a radical selected from the group consisting of halo, C_{1-2} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, aryl, heteroaryl, oxo, cyano, carboxyl, cyano-C_{1-3}-alkyl, heterocyclyloxy, C_{1-3} alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, phenyl, C_{1-3} haloalkyl, heterocyclo, cycloalkenyl, phenyl-C_{1-3}-alkyl, heterocyclyl-C_{1-3}-alkyl, C_{1-3} alkylthio-C_{1-3}-alkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxycarbonyl, phenylcarbonyl, phenyl-C_{1-3}-alkylcarbonyl, phenyl-C_{2-3}-alkenyl, C_{1-3} alkoxy-C_{1-3}-alkyl, phenylthio-C_{1-3}-alkyl, phenylyloxyalkyl, alkoxyphenylalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonyl-C_{1-3}-alkyl, C_{1-3} alkylaminocarbonyl, N-phenylaminocarbonyl, N-C_{1-3} alkyl-N-phenylaminocarbonyl, C_{1-3} alkylaminocarbonyl-C_{1-3}-alkyl, carboxy-C_{1-3}-alkyl, C_{1-3} alkylamino, N-arylamino, N-arylkylamino, N-C_{1-3} alkyl-N-arylkylamino, N-C_{1-3} alkyl-N-arylamino, amino-C_{1-3}-alkyl, C_{1-3} alkylaminoalkyl, N-phenylamino-C_{1-3}-alkyl, N-phenyl-C_{1-3}-alkylaminoalkyl, N-C_{1-3} alkyl-N-phenyl-C_{1-3}-alkylamino-C_{1-3}-alkyl, N-C_{1-3} alkyl-N-phenylamino-C_{1-3}-alkyl, phenyloxy, phenylalkoxy, phenylthio, phenyl-C_{1-3}-alkylthio, C_{1-3} alkylsulfinyl, C_{1-3} alkylsulfonyl, aminosulfonyl, C_{1-3} alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-C_{1-3} alkyl-N-phenylaminosulfonyl.

107. The method of claim 106 wherein R^3 is a radical selected from the group consisting of halo, C_{1-2} alkyl, cyano, carboxyl, C_{1-2} alkyloxy, phenyl, C1-2 haloalkyl, and C_{1-2} hydroxyalkyl.

108. The method of claim 73 wherein R^4 is hydrido.

109. The method of claim 73 wherein R^4 is halo.

110. The method of claim 109 wherein the halo is fluoro.

111. The method of claim 73 wherein the selective cyclooxygenase-2 inhibiting agent is 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide,

112. The method of claim 73 wherein the selective cyclooxygenase-2 inhibiting agent is 4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone.

113. The method of claim 73 wherein the selective cyclooxygenase-2 inhibiting agent is 2-(6-methylpyrid-3-yl)-3-(4-methylsulfinylphenyl)-5-chloropyridine.

114. The method of claim 7 wherein the selective cyclooxygenase-2 inhibiting agent is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide.

115. The method of claim 73 wherein the selective cyclooxygenase-2 inhibiting agent is 4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone.

116. The method of claim 73 wherein the selective cyclooxygenase-2 inhibiting agent is 4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide.

117. The method of claim 73 wherein the selective cyclooxygenase-2 inhibiting agent is 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide.

118. The method of claim 73 wherein the selective cyclooxygenase-2 inhibiting agent is 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine.

119. The method of claim 73 wherein the selective cyclooxygenase-2 inhibiting agent is 2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one.

120. The method of claim 73 wherein the selective cyclooxygenase-2 inhibiting agent is 4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone.

121. The method of claim 73 wherein the selective cyclooxygenase-2 inhibiting agent is 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide.

122. The method of claim 73 wherein the selective cyclooxygenase-2 inhibiting agent is N-[[4-(5-methyl-3-phenylisoxazol-4-yl]phenyl]sulfonyl]propanamide.

123. The method of claim 67 wherein the agents are administered in a sequential manner.

124. The method of claim 67 wherein the agents are administered in a substantially simultaneous manner.

125. The method of claim 67 wherein the tumor necrosis factor antagonizing agent is administered parentally.

126. The method of claim 125 wherein the parental administration is by intravenous injection, subcutaneous injection, intramuscular injection, or intramedullary injection.

127. The method of claim 67 wherein the cyclooxygenase-2 inhibiting agent and the tumor necrosis factor antagonizing agent are formulated in a single composition.

128. The method of claim 67 wherein the cyclooxygenase-2 inhibiting agent and the tumor necrosis factor antagonizing agent each are provided as a separate component of a kit.

129. The method of claim 67 wherein the inflammatory disorder is selected from the group consisting of rheumatoid arthritis, osteoarthritis, spondylarthropy, ankylosing spondylitis, psoriatic arthritis, reactive arthritis, IBD related arthritis, undifferentiated spondyloarthropathy, Reider's syndrome, systemic lupus erythematosus, Behcet's disease, eosinophilia fasciitis, eosinophila-myalgia syndrome, familial Mediterranean fever, hereditary angioedema, juvenile chronic arthritis, palindromic rheumatism, idiopathic polymyositis, dermatomyositis, inclusion body myositis, systemic sclerosis, atherosclerosis, sarcoidisis, Reynaud's phenomenon, Sjogren's syndrome, Still's disease, systemic rheumatoid vasculitis, vasculitis, Wegener's granulomatosis, Whipple's disease, and xerostomia.

130. The method of claim 129 wherein the inflammatory disorder is selected from the group consisting of rheumatoid arthritis, and osteoarthritis.

131. The method of claim 130 wherein the inflammatory disorder is rheumatoid arthritis.

132. A method of use of a composition in preparation of a medicament useful in treating an inflammatory disorder in a mammal in need thereof, the composition comprising a tumor necrosis factor antagonizing agent and a cylcooxygenase-2 inhibitor, wherein the agents together comprise an inflammatory disorder effective amount of the agents.

133. The method of claim 132 wherein the tumor necrosis factor antagonizing agent is a protein.

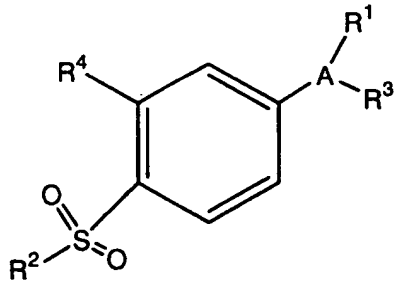
134. The method of claim 133 wherein the protein competitively binds to a cell surface tumor necrosis factor receptor.

135. The method of claim 133 wherein the protein competitively binds to an intracellular tumor necrosis factor receptor.

136. The method of claim 133 wherein the tumor necrosis factor antagonizing agent is etanercept.

137. The method of claim 132 wherein the tumor necrosis factor antagonizing agent is selected from the group consisting of 2-[(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)methylene]-undecanoic acid; etanercept; lenercept; BB-2275; PCM-4; SH-636; onercept; TBP-1; solimastat; MDL-201112; AGT-1; D-609; 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-pyrrolidinone; CytoTAb®; and Infliximab.

138. The method of claim 132 wherein the selective cyclooxygenase-2 inhibiting agent is selected from compounds of Formula 1:



1.

wherein

A is a 5- or 6-member ring substituent selected from partially unsaturated or unsaturated heterocyclo and carboxcyclic rings, wherein A is optionally substituted with one or more radicals selected from the group consisting of alkyl, halo, oxo, and alkoxy;

R^1 is selected from the group consisting of cyclohexyl, pyridinyl, and phenyl, wherein cyclohexyl, pyridinyl, or phenyl are optionally substituted with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, phenylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio;

R^2 is selected from the group consisting of alkyl and amino;

R^3 is a radical selected from the group consisting of halo, alkyl, alkenyl, alkynyl, aryl, heteroaryl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, phenyl, haloalkyl, heterocyclo, cycloalkenyl, phenylalkyl, heterocyclylalkyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, phenylcarbonyl, phenylalkylcarbonyl, phenylalkenyl, alkoxyalkyl, phenylthioalkyl, phenylyloxyalkyl, alkoxyphenylalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-phenylaminocarbonyl, N-alkyl-N-phenylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-arylkylamino, N-alkyl-N-arylkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-phenylaminoalkyl, N-phenylalkylaminoalkyl, N-alkyl-N-phenylalkylaminoalkyl, N-alkyl-N-phenylaminoalkyl, phenyloxy, phenylalkoxy, phenylthio, phenylalkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-alkyl-N-phenylaminosulfonyl; and

R^4 is selected from the group consisting of hydrido and halo;

or a pharmaceutically-acceptable salt thereof.

139. The method of claim 138 wherein A is selected from the group consisting of thienyl, oxazolyl, furyl, furanone, pyrrolyl, thiazolyl, imidazolyl, benzofuryl, indenyl, benzithienyl, isoxazolyl, pyrazolyl, cyclopentenyl, cyclopentadienyl, benzindazolyl, cyclopentenone, benzopyranopyrazolyl, phenyl, and pyridyl.

140. The method of claim 139 wherein A is substituted with one or more radicals selected from the group consisting of alkyl, halo, oxo, and alkoxy.

141. The method of claim 140 wherein A is substituted with halo.

142. The method of claim 141 wherein the halo is choro.

143. The method of claim 141 wherein A is substituted by alkyl.

144. The method of claim 143 wherein the alkyl is methyl.

145. The method of claim 140 wherein A is substituted with oxo.

146. The method of claim 140 wherein A is substituted with alkoxy.

147. The method of claim 138 wherein R^1 is selected from the group consisting of cyclohexyl, pyridinyl, and phenyl, wherein cyclohexyl, pyridinyl, or phenyl is substituted with one or more radicals selected from C_{1-2} alkyl, C_{1-2} haloalkyl, cyano, carboxyl, C_{1-2} alkoxycarbonyl, hydroxyl, C_{1-2} hydroxyalkyl, C_{1-2} haloalkoxy, amino, C_{1-2} alkylamino, phenylamino, nitro, C_{1-2} alkoxy-C_{1-2}-alkyl, C_{1-2} alkylsulfinyl, C_{1-2} alkoxy, halo, alkoxy, and C_{1-2} alkylthio.

148. The method of claim 138 wherein R^1 is selected from the group consisting of pyridyl, cyclohexyl, and phenyl, wherein pyridyl, cyclohexyl, or phenyl is optionally substituted with one or more radicals selected from the group consisting of alkyl, halo, and alkoxy.

149. The method of claim 148 wherein R^1 is pyridyl.

150. The method of claim 149 wherein pyridyl is substituted with one or more radicals selected from the group consisting of alkyl, halo, and alkoxy.

151. The method of claim 150 wherein the pyridyl is substituted with alkyl.

152. The method of claim 151 wherein alkyl is C_{1-2} alkyl.

153. The method of claim 152 wherein alkyl is methyl.

154. The method of claim 150 wherein the pyridyl is substituted with halo.

155. The method of claim 154 wherein the halo is chloro.

156. The method of claim 144 wherein R^1 is cyclohexyl.

157. The method of claim 156 wherein the cyclohexyl is substituted with one or more radicals selected from the group consisting of alkyl, halo, and alkoxy.

158. The method of claim 156 wherein the cyclohexyl is substituted with alkyl.

159. The method of claim 158 wherein the alkyl is C_{1-2} alkyl.

160. The method of claim 159 wherein the alkyl is methyl.

161. The method of claim 156 wherein the pyridyl is substituted with halo.

162. The method of claim 161 wherein the halo is chloro.

163. The method of claim 148 wherein R^1 is phenyl.

164. The method of claim 163 wherein the phenyl is substituted with one or more radicals selected from the group consisting of alkyl, halo, and alkoxy.

165. The method of claim 164 wherein the phenyl is substituted with alkyl.

166. The method of claim 165 wherein the alkyl is C_{1-2} alkyl.

167. The method of claim 166 wherein the alkyl is methyl.

168. The method of claim 138 wherein R^2 is alkyl or amino.

169. The method of claim 168 wherein the alkyl is C_{1-2} alkyl.

170. The method of claim 169 wherein the alkyl is methyl.

171. The method of claim 138 wherein R^3 is a radical selected from the group consisting of halo, C_{1-2} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, aryl, heteroaryl, oxo, cyano, carboxyl, cyano-C_{1-3}-alkyl, heterocyclyloxy, C_{1-3} alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, phenyl, C_{1-3} haloalkyl, heterocyclo, cycloalkenyl, phenyl-C_{1-3}-alkyl, heterocyclyl-C_{1-3}-alkyl, C_{1-3} alkylthio-C_{1-3}-alkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxycarbonyl, phenylcarbonyl, phenyl-C_{1-3}-alkylcarbonyl, phenyl-C_{2-3}-alkenyl, C_{1-3} alkoxy-C_{1-3}-alkyl, phenylthio-C_{1-3}-alkyl, phenylyloxyalkyl, alkoxyphenylalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonyl-C_{1-3}-alkyl, C_{1-3} alkylaminocarbonyl, N-phenylaminocarbonyl, N-C_{1-3} alkyl-N-phenylaminocarbonyl, C_{1-3} alkylaminocarbonyl-C_{1-3}-alkyl, carboxy-C_{1-3}-alkyl, C_{1-3} alkylamino, N-arylamino, N-arylkylamino, N-C_{1-3} alkyl-N-arylkylamino, N-C_{1-3} alkyl-N-arylamino, amino-C_{1-3}-alkyl, C_{1-3} alkylaminoalkyl, N-phenylamino-C_{1-3}-alkyl, N-phenyl-C_{1-3}-alkylaminoalkyl, N-C_{1-3} alkyl-N-phenyl-C_{1-3}-alkylamino-C_{1-3}-alkyl, N-C_{1-3} alkyl-N-phenylamino-C_{1-3}-alkyl, phenyloxy, phenylalkoxy, phenylthio, phenyl-C_{1-3}-alkylthio, C_{1-3} alkylsulfinyl, C_{1-3} alkylsulfonyl, aminosulfonyl, C_{1-3} alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-C_{1-3} alkyl-N-phenylaminosulfonyl.

172. The method of claim 171 wherein R^3 is a radical selected from the group consisting of halo, C_{1-2} alkyl, cyano, carboxyl, C_{1-2} alkyloxy, phenyl, C1-2 haloalkyl, and C_{1-2} hydroxyalkyl.

173. The method of claim 138 wherein R^4 is hydrido.

174. The method of claim 138 wherein R^4 is halo.

175. The method of claim 174 wherein the halo is fluoro.

176. The method of claim 138 wherein the selective cyclooxygenase-2 inhibiting agent is 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide,

177. The method of claim 138 wherein the selective cyclooxygenase-2 inhibiting agent is 4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone.

178. The method of claim 138 wherein the selective cyclooxygenase-2 inhibiting agent is 2-(6-methylpyrid-3-yl)-3-(4-methylsulfinylphenyl)-5-chloropyridine.

179. The method of claim 138 wherein the selective cyclooxygenase-2 inhibiting agent is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide.

180. The method of claim 138 wherein the selective cyclooxygenase-2 inhibiting agent is 4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone.

181. The method of claim 138 wherein the selective cyclooxygenase-2 inhibiting agent is 4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide.

182. The method of claim 138 wherein the selective cyclooxygenase-2 inhibiting agent is 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide.

183. The method of claim 138 wherein the selective cyclooxygenase-2 inhibiting agent is 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine.

184. The method of claim 138 wherein the selective cyclooxygenase-2 inhibiting agent is 2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one.

185. The method of claim 138 wherein the selective cyclooxygenase-2 inhibiting agent is 4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone.

186. The method of claim 138 wherein the selective cyclooxygenase-2 inhibiting agent is 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide.

187. The method of claim 138 wherein the selective cyclooxygenase-2 inhibiting agent is N-[[4-(5-methyl-3-phenylisoxazol-4-yl]phenyl]sulfonyl]propanamide.

188. The method of claim 132 wherein the agents are administered in a sequential manner.

189. The method of claim 132 wherein the agents are administered in a substantially simultaneous manner.

190. The method of claim 132 wherein the tumor necrosis factor antagonizing agent is administered parentally.

191. The method of claim 190 wherein the parental administration is by intravenous injection, subcutaneous injection, intramuscular injection, or intramedullary injection.

192. The method of claim 132 wherein the cyclooxygenase-2 inhibiting agent and the tumor necrosis factor antagonizing agent are formulated in a single composition.

193. The method of claim 132 wherein the cyclooxygenase-2 inhibiting agent and the tumor necrosis factor antagonizing agent each are provided as a separate component of a kit.

194. The method of claim 132 wherein the inflammatory disorder is selected from the group consisting of rheumatoid arthritis, osteoarthritis, spondylarthropy, ankylosing spondylitis, psoriatic arthritis, reactive arthritis, IBD related arthritis, undifferentiated spondyloarthropathy, Reider's syndrome, systemic lupus erythematosus, Behcet's disease, eosinophilia fasciitis, eosinophila-myalgia syndrome, familial Mediterranean fever, hereditary angioedema, juvenile chronic arthritis, palindromic rheumatism, idiopathic polymyositis, dermatomyositis, inclusion body

myositis, systemic sclerosis, atherosclerosis, sarcoidisis, Reynaud's phenomenon, Sjogren's syndrome, Still's disease, systemic rheumatoid vasculitis, vasculitis, Wegener's granulomatosis, Whipple's disease, and xerostomia.

195. The method of claim 194 wherein the inflammatory disorder is selected from the group consisting of rheumatoid arthritis, and osteoarthritis.

196. The method of claim 195 wherein the inflammatory disorder is rheumatoid arthritis.

197. A pharmaceutical composition comprising an inflammatory disorder effective amount of a tumor necrosis factor antagonizing agent and a cylcooxygenase-2 inhibitor.

198. The pharmaceutical composition of claim 197 wherein the tumor necrosis factor antagonizing agent is a protein.

199. The pharmaceutical composition of claim 198 wherein the protein competitively binds to a cell surface tumor necrosis factor receptor.

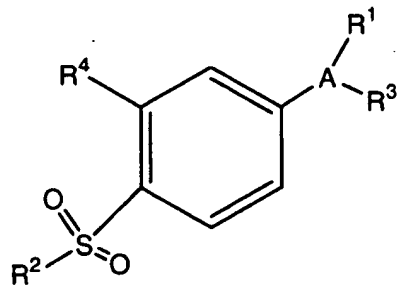
200. The pharmaceutical composition of claim 198 wherein the protein competitively binds to an intracellular tumor necrosis factor receptor.

201. The pharmaceutical composition of claim 198 wherein the tumor necrosis factor antagonizing agent is etanercept.

202. The pharmaceutical composition of claim 197 wherein the tumor necrosis factor antagonizing agent is selected from the group consisting of 2-[(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)methylene]-undecanoic acid; lenercept; BB-2275; PCM-4; SH-636; onercept; TBP-1; etanercept; solimastat; MDL-201112; AGT-1; D-609; 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-pyrrolidinone; CytoTAb®; and Infliximab.

92

203. The pharmaceutical composition of claim 197 wherein the selective cyclooxygenase-2 inhibiting agent is selected from compounds of Formula 1:



1.

wherein

A is a 5- or 6-member ring substituent selected from partially unsaturated or unsaturated heterocyclo and carboxcyclic rings, wherein A is optionally substituted with one or more radicals selected from the group consisting of alkyl, halo, oxo, and alkoxy;

R^1 is selected from the group consisting of cyclohexyl, pyridinyl, and phenyl, wherein cyclohexyl, pyridinyl, or phenyl are optionally substituted with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, phenylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio;

R^2 is selected from the group consisting of alkyl and amino;

R^3 is a radical selected from the group consisting of halo, alkyl, alkenyl, alkynyl, aryl, heteroaryl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, phenyl, haloalkyl, heterocyclo, cycloalkenyl, phenylalkyl, heterocyclylalkyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, phenylcarbonyl, phenylalkylcarbonyl, phenylalkenyl, alkoxyalkyl, phenylthioalkyl, phenylyloxyalkyl, alkoxyphenylalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-phenylaminocarbonyl, N-alkyl-N-phenylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-arylkylamino, N-alkyl-N-arylkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-phenylaminoalkyl, N-phenylalkylaminoalkyl, N-alkyl-N-phenylalkylaminoalkyl, N-alkyl-N-phenylaminoalkyl, phenyloxy, phenylalkoxy, phenylthio, phenylalkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl,

alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-alkyl-N-phenylaminosulfonyl; and

R^4 is selected from the group consisting of hydrido and halo;

or a pharmaceutically-acceptable salt thereof.

204. The pharmaceutical composition of claim 203 wherein A is selected from the group consisting of thienyl, oxazolyl, furyl, furanone, pyrrolyl, thiazolyl, imidazolyl, benzofuryl, indenyl, benzithienyl, isoxazolyl, pyrazolyl, cyclopentenyl, cyclopentadienyl, benzindazolyl, cyclopentenone, benzopyranopyrazolyl, phenyl, and pyridyl.

205. The pharmaceutical composition of claim 204 wherein A is substituted with one or more radicals selected from the group consisting of alkyl, halo, oxo, and alkoxy.

206. The pharmaceutical composition of claim 205 wherein A is substituted with halo.

207. The pharmaceutical composition of claim 206 wherein the halo is choro.

208. The pharmaceutical composition of claim 205 wherein A is substituted by alkyl.

209. The pharmaceutical composition of claim 208 wherein the alkyl is methyl.

210. The pharmaceutical composition of claim 205 wherein A is substituted with oxo.

211. The pharmaceutical composition of claim 205 wherein A is substituted with alkoxy.

212. The pharmaceutical composition of claim 203 wherein R^1 is selected from the group consisting of cyclohexyl, pyridinyl, and phenyl, wherein cyclohexyl, pyridinyl, or phenyl is substituted with one or more radicals selected from C_{1-2} alkyl, C_{1-2} haloalkyl, cyano, carboxyl, C_{1-2} alkoxycarbonyl, hydroxyl, C_{1-2} hydroxyalkyl, C_{1-2} haloalkoxy, amino, C_{1-2} alkylamino, phenylamino, nitro, C_{1-2} alkoxy-C_{1-2}-alkyl, C_{1-2} alkylsulfinyl, C_{1-2} alkoxy, halo, alkoxy, and C_{1-2} alkylthio.

213. The pharmaceutical composition of claim 203 wherein R^1 is selected from the group consisting of pyridyl, cyclohexyl, and phenyl, wherein pyridyl, cyclohexyl, or phenyl is optionally substituted with one or more radicals selected from the group consisting of alkyl, halo, and alkoxy.

214. The pharmaceutical composition of claim 213 wherein R^1 is pyridyl.

215. The pharmaceutical composition of claim 214 wherein pyridyl is substituted with one or more radicals selected from the group consisting of alkyl, halo, and alkoxy.

216. The pharmaceutical composition of claim 215 wherein the pyridyl is substituted with alkyl.

217. The pharmaceutical composition of claim 216 wherein alkyl is C_{1-2} alkyl.

218. The pharmaceutical composition of claim 217 wherein alkyl is methyl.

219. The pharmaceutical composition of claim 215 wherein the pyridyl is substituted with halo.

220. The pharmaceutical composition of claim 219 wherein the halo is chloro.

221. The pharmaceutical composition of claim 213 wherein R^1 is cyclohexyl.

222. The pharmaceutical composition of claim 221 wherein the cyclohexyl is substituted with one or more radicals selected from the group consisting of alkyl, halo, and alkoxy.

223. The pharmaceutical composition of claim 221 wherein the cyclohexyl is substituted with alkyl.

224. The pharmaceutical composition of claim 223 wherein the alkyl is C_{1-2} alkyl.

225. The pharmaceutical composition of claim 224 wherein the alkyl is methyl.

226. The pharmaceutical composition of claim 221 wherein the pyridyl is substituted with halo.

227. The pharmaceutical composition of claim 226 wherein the halo is chloro.

228. The pharmaceutical composition of claim 213 wherein R^1 is phenyl.

229. The pharmaceutical composition of claim 228 wherein the phenyl is substituted with one or more radicals selected from the group consisting of alkyl, halo, and alkoxy.

230. The pharmaceutical composition of claim 229 wherein the phenyl is substituted with alkyl.

231. The pharmaceutical composition of claim 230 wherein the alkyl is C_{1-2} alkyl.

232. The pharmaceutical composition of claim 231 wherein the alkyl is methyl.

233. The pharmaceutical composition of claim 203 wherein R^2 is alkyl or amino.

234. The pharmaceutical composition of claim 233 wherein the alkyl is C_{1-2} alkyl.

235. The pharmaceutical composition of claim 234 wherein the alkyl is methyl.

236. The pharmaceutical composition of claim 203 wherein R^3 is a radical selected from the group consisting of halo, C_{1-2} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, aryl, heteroaryl, oxo, cyano, carboxyl, cyano-C_{1-3}-alkyl, heterocyclyloxy, C_{1-3} alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, phenyl, C_{1-3} haloalkyl, heterocyclo, cycloalkenyl, phenyl-C_{1-3}-alkyl, heterocyclyl-C_{1-3}-alkyl, C_{1-3} alkylthio-C_{1-3}-alkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxycarbonyl, phenylcarbonyl, phenyl-C_{1-3}-alkylcarbonyl, phenyl-C_{2-3}-alkenyl, C_{1-3} alkoxy-C_{1-3}-alkyl, phenylthio-C_{1-3}-alkyl, phenylyloxyalkyl, alkoxyphenylalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonyl-C_{1-3}-alkyl, C_{1-3} alkylaminocarbonyl, N-phenylaminocarbonyl, N-C_{1-3} alkyl-N-phenylaminocarbonyl, C_{1-3} alkylaminocarbonyl-C_{1-3}-alkyl, carboxy-C_{1-3}-alkyl, C_{1-3} alkylamino, N-arylamino, N-arylkylamino, N-C_{1-3} alkyl-N-arylkylamino, N-C_{1-3} alkyl-N-arylamino, amino-C_{1-3}-alkyl, C_{1-3} alkylaminoalkyl, N-phenylamino-C_{1-3}-alkyl, N-phenyl-C_{1-3}-alkylaminoalkyl, N-C_{1-3} alkyl-N-phenyl-C_{1-3}-alkylamino-C_{1-3}-alkyl, N-C_{1-3} alkyl-N-phenylamino-C_{1-3}-alkyl, phenyloxy, phenylalkoxy, phenylthio, phenyl-C_{1-3}-alkylthio, C_{1-3} alkylsulfinyl, C_{1-3} alkylsulfonyl, aminosulfonyl, C_{1-3} alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-C_{1-3} alkyl-N-phenylaminosulfonyl.

237. The pharmaceutical composition of claim 236 wherein R^3 is a radical selected from the group consisting of halo, C_{1-2} alkyl, cyano, carboxyl, C_{1-2} alkyloxy, phenyl, C1-2 haloalkyl, and C_{1-2} hydroxyalkyl.

238. The pharmaceutical composition of claim 203 wherein R^4 is hydrido.

239. The pharmaceutical composition of claim 203 wherein R^4 is halo.

240. The pharmaceutical composition of claim 239 wherein the halo is fluoro.

241. The pharmaceutical composition of claim 203 wherein the selective cyclooxygenase-2 inhibiting agent is 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide,

242. The pharmaceutical composition of claim 203 wherein the selective cyclooxygenase-2 inhibiting agent is 4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone.

243. The pharmaceutical composition of claim 203 wherein the selective cyclooxygenase-2 inhibiting agent is 2-(6-methylpyrid-3-yl)-3-(4-methylsulfinylphenyl)-5-chloropyridine.

244. The pharmaceutical composition of claim 203 wherein the selective cyclooxygenase-2 inhibiting agent is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide.

245. The pharmaceutical composition of claim 203 wherein the selective cyclooxygenase-2 inhibiting agent is 4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone.

246. The pharmaceutical composition of claim 203 wherein the selective cyclooxygenase-2 inhibiting agent is 4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide.

247. The pharmaceutical composition of claim 203 wherein the selective cyclooxygenase-2 inhibiting agent is 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide.

248. The pharmaceutical composition of claim 203 wherein the selective cyclooxygenase-2 inhibiting agent is 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine.

249. The pharmaceutical composition of claim 203 wherein the selective cyclooxygenase-2 inhibiting agent is 2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one.

250. The pharmaceutical composition of claim 203 wherein the selective cyclooxygenase-2 inhibiting agent is 4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone.

251. The pharmaceutical composition of claim 203 wherein the selective cyclooxygenase-2 inhibiting agent is 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide.

252. The pharmaceutical composition of claim 203 wherein the selective cyclooxygenase-2 inhibiting agent is N-[[4-(5-methyl-3-phenylisoxazol-4-yl]phenyl]sulfonyl]propanamide.

253. The pharmaceutical composition of claim 197 wherein the agents are administered in a sequential manner.

254. The pharmaceutical composition of claim 197 wherein the agents are administered in a substantially simultaneous manner.

255. The pharmaceutical composition of claim 197 wherein the tumor necrosis factor antagonizing agent is administered parentally.

256. The pharmaceutical composition of claim 255 wherein the parental administration is byintravenous injection, subcutaneous injection, intramuscular injection, or intramedullary injection.

257. The method of claim 197 wherein the cyclooxygenase-2 inhibiting agent and the tumor necrosis factor antagonizing agent are formulated in a single composition.

258. The pharmaceutical composition of claim 197 wherein the cyclooxygenase-2 inhibiting agent and the tumor necrosis factor antagonizing agent each are provided as a separate component of a kit.

259. The pharmaceutical composition of claim 197 wherein the inflammatory disorder is selected from the group consisting of rheumatoid arthritis, osteoarthritis, spondylarthropy, ankylosing spondylitis, psoriatic arthritis, reactive arthritis, IBD related arthritis, undifferentiated spondyloarthropathy, Reider's syndrome, systemic lupus erythematosus, Behcet's disease, eosinophilia fasciitis, eosinophila-myalgia syndrome, familial Mediterranean fever, hereditary angioedema, juvenile chronic arthritis, palindromic rheumatism, idiopathic polymyositis, dermatomyositis, inclusion body myositis, systemic sclerosis, sarcoidisis, Reynaud's phenomenon, Sjogren's syndrome, Still's disease, systemic rheumatoid vasculitis, systemic sclerosis, vasculitis, Wegener's granulomatosis, Whipple's disease, and xerostomia.

260. The pharmaceutical composition of claim 259 wherein the inflammatory disorder is selected from the group consisting of rheumatoid arthritis, and osteoarthritis.

261. The pharmaceutical composition of claim 259 wherein the inflammatory disorder is rheumatoid arthritis.

262. The pharmaceutical composition of claim 197 wherein the composition is provided as a separate component of a kit.

263. The pharmaceutical composition of claim 197 wherein the composition is administered orally.

264. The pharmaceutical composition of claim 197 wherein the composition is administered intravascularly.

265. The pharmaceutical composition of claim 197 wherein the composition is administered intraperitoneally.

266. The pharmaceutical composition of claim 197 wherein the composition is administered subcutaneously.

267. The pharmaceutical composition of claim 197 wherein the composition is administered topically.

268. The pharmaceutical composition of claim 197 wherein the composition is administered parenterally.

269. The pharmaceutical composition of claim 197 wherein the composition is administered as a gel, a spray, an ointment, a cream or a suppository.

270. The pharmaceutical composition of claim 197 wherein the composition is administered transdermally.

271. The pharmaceutical composition of claim 197 wherein the composition is selected from the group consisting of a tablet, a capsule, a cachet, a lozenge, a dispensable powder, a granule, a solution, a suspension, an emulsion, and a liquid.

272. The pharmaceutical composition of claim 197 wherein the selective cyclooxygenase-2 inhibiting agent is present in an amount from about 0.1 mg to about 10,000 mg.

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/US 00/16292

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/19 A61K31/63

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
MEDLINE, BIOSIS, EMBASE, EPO-Internal, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KUMAR, ANIL (1) ET AL: "Analgesic and anti-inflammatory effects of phosphodiesterase inhibitors." INDIAN JOURNAL OF EXPERIMENTAL BIOLOGY, (JAN., 1999) VOL. 38, NO. 1, PP. 26-30. , XP000972082 abstract; figure 3 --- -/--	1-272

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 December 2000	08/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gonzalez Ramon, N

3

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	MORELAND L W ET AL: "TREATMENT OF RHEUMATOID ARTHRITIS WITH A RECOMBINANT HUMAN TUMOR NECROSIS FACTOR RECEPTOR (P75)-FC FUSION PROTEIN" NEW ENGLAND JOURNAL OF MEDICINE, THE,MASSACHUSETTS MEDICAL SOCIETY, WALTHAM, MA,US, vol. 337, no. 3, 17 July 1997 (1997-07-17), pages 141-147, XP000946860 ISSN: 0028-4793 page 142, paragraph 2; table 1 ---	1-272
T	BRAUN J. ET AL: "Anti- TNF.alpha: A new dimension in the pharmacotherapy of the spondyloarthropathies ?." ANNALS OF THE RHEUMATIC DISEASES, (2000) 59/6 (404-406). , XP000972114 page 404 ---	1-272
X	MORELAND L. W. ET AL: "Etanercept therapy in rheumatoid arthritis" ANN INTERN MED, vol. 130, no. 6, 1999, pages 478-486, XP000965589 page 479, column 1; table 1 page 481, column 2, paragraph 3 ---	1-272
Y,P	SIMON L.S. ET AL: "New and future drug therapies for rheumatoid arthritis" RHEUMATOLOGY, vol. 39, no. sup1, June 2000 (2000-06), pages 36-42, XP000965563 abstract page 40 -page 41 ---	1-272
X,P	LORENZ H.M. ET AL: "Biological agents: a novel approach to the therapy of rheumatoid arthritis" EXP. OPIN. INVEST. DRUGS, July 2000 (2000-07), pages 1479-1490, XP000965599 abstract page 1486 ---	1-272
P,X	EP 0 927 555 A (SANKYO CO) 7 July 1999 (1999-07-07) page 2, line 20-25 page 4 -page 5; claim 42 ---	1-272
E	WO 00 48583 A (POZEN INC) 24 August 2000 (2000-08-24) abstract; claims 11-15 ---	1-272

-/--

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/US 00/16292

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 731 343 A (FENG LILI ET AL) 24 March 1998 (1998-03-24) abstract; claim 4; figures 13B,14; example 6; table 1	1-272
A	US 5 605 690 A (SMITH CRAIG A ET AL) 25 February 1997 (1997-02-25) abstract	1-272
Y	WO 98 16227 A (GORDON GARY B ;SEARLE & CO (US); SEIBERT KAREN (US); MASFERRER JAI) 23 April 1998 (1998-04-23) abstract page 23 -page 28	1-272
A	US 5 795 967 A (AGGARWAL BHARAT B ET AL) 18 August 1998 (1998-08-18) abstract	1-272

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0927555 A	07-07-1999	AU 9822598 A	15-07-1999
		BR 9805544 A	28-03-2000
		CN 1230407 A	06-10-1999
		CZ 9804258 A	14-07-1999
		HU 9803018 A	28-10-1999
		JP 11246403 A	14-09-1999
		NO 986089 A	25-06-1999
		PL 330496 A	05-07-1999
		ZA 9811840 A	23-06-1999
		JP 11279078 A	12-10-1999
		JP 2000095685 A	04-04-2000
		JP 2000159690 A	13-06-2000
WO 0048583 A	24-08-2000	NONE	
US 5731343 A	24-03-1998	AU 5175296 A	11-09-1996
		CA 2213632 A	29-08-1996
		EP 0810860 A	10-12-1997
		WO 9625928 A	29-08-1996
US 5605690 A	25-02-1997	US 5395760 A	07-03-1995
		AU 670125 B	04-07-1996
		AU 4920993 A	12-04-1994
		CA 2123593 A	31-03-1994
		EP 0620739 A	26-10-1994
		JP 7504203 T	11-05-1995
		KR 232688 B	01-12-1999
		NO 941780 A	15-07-1994
		NZ 256293 A	24-06-1997
		WO 9406476 A	31-03-1994
		AT 131871 T	15-01-1996
		DE 69024291 D	01-02-1996
		DE 69024291 T	31-10-1996
		DK 418014 T	22-01-1996
		EP 0418014 A	20-03-1991
		ES 2080809 T	16-02-1996
		GR 3019333 T	30-06-1996
		IE 63505 B	03-05-1995
		JP 2960039 B	06-10-1999
		JP 10191986 A	28-07-1998
		JP 2721745 B	04-03-1998
		JP 3133382 A	06-06-1991
		LU 90591 A	31-07-2000
		MX 9203660 A	01-07-1992
		NZ 235148 A	23-12-1991
		US RE36755 E	27-06-2000
		US 5712155 A	27-01-1998
		US 5945397 A	31-08-1999
		AU 630497 B	29-10-1992
		AU 6178190 A	08-04-1991
		CA 2065346 A	06-03-1991
		FI 105099 B	15-06-2000
		FI 20000833 A	07-04-2000
		NO 920862 A	04-05-1992
		WO 9103553 A	21-03-1991
		DD 297664 A	16-01-1992
		ZA 9007072 A	30-10-1991

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9816227 A	23-04-1998	AU 4904897 A	11-05-1998
		BR 9712314 A	31-08-1999
		CN 1244122 A	09-02-2000
		CZ 9901171 A	14-07-1999
		EP 0932402 A	04-08-1999
		NO 991793 A	15-04-1999
		SK 46299 A	13-03-2000
US 5795967 A	18-08-1998	US 5672347 A	30-09-1997
		MX 9203709 A	01-09-1992
		AT 113295 T	15-11-1994
		AU 599571 B	26-07-1990
		AU 4465285 A	09-01-1986
		BG 60250 B	24-03-1994
		CZ 8505067 A	16-07-1997
		DE 3587939 D	01-12-1994
		DE 3587939 T	27-04-1995
		DK 75694 A	24-06-1994
		DK 305885 A	14-03-1986
		EP 0168214 A	15-01-1986
		FI 852626 A,B,	06-01-1986
		FI 943750 A,B,	15-08-1994
		GR 851626 A	26-11-1985
		HR 950156 A	31-08-1997
		HU 209153 B	28-03-1994
		IE 65426 B	01-11-1995
		IL 75717 A	28-11-1994
		IL 105271 A	31-07-1995
		JP 7291997 A	07-11-1995
		JP 2614989 B	28-05-1997
		JP 8003061 A	09-01-1996
		JP 2557341 B	27-11-1996
		JP 61040221 A	26-02-1986
		JP 9028387 A	04-02-1997
		KR 9310767 B	10-11-1993
		LU 90456 A	06-12-1999
		NO 852673 A	06-01-1986
		NZ 212632 A	28-05-1991
		PL 254399 A	17-06-1986
		PT 80758 A,B	01-08-1985
		SI 8511132 A,B	31-10-1996
		SK 506785 A	07-05-1999
		YU 113285 A	30-04-1991
		ES 544843 D	01-05-1988
		ES 8802250 A	01-07-1988
		ES 557105 D	16-12-1987
		ES 8800984 A	16-02-1988